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Table 1. Summary of major formaldehyde carcinogenicity classifications and noted scientific basis

Year	Agency	Carcinogenicity Classification	Findings
1981	NTP (2nd Report on Carcinogens, 1981)	Anticipated to be a human carcinogen	**Epidemiological evidence.** Not discussed
			Toxicological evidence. One study cited (Swenberg et al. 1980). "While a full evaluation of the carcinogenicity of formaldehyde vapor must await completion of studies at the Chemical Industry Institute of Toxicology, evidence presented to date demonstrates that inhalation of formaldehyde results in a high incidence of nasal cancers in rats (Swenberg et al. 1980)."
1981 [a]	IARC (Monograph Volume 29, 1982 and Monograph Suppl 4, 1982)	Probably carcinogenic to humans (Group 2B)	**Epidemiological evidence. Inadequate** (6 epidemiology studies)
			Toxicological evidence. Sufficient, formaldehyde is carcinogenic to rat, causes nasal cancers.
1982	NTP (3rd RoC 1982)	Anticipated to be a human carcinogen	**Epidemiological evidence.** Inadequate (cites IARC, 1982, Suppl 4, IARC, 1982, Volume 29)
			Toxicological evidence. Sufficient, formaldehyde is carcinogenic to two strains of rats. Nasal cancers. One test in mice did not produce statistically significant results. Other studies in animals (mice and hamsters by inhalation exposure) were considered inadequate for evaluation.
1987 [b]	IARC (Monograph Suppl 7, 1987)	Probably carcinogenic to humans (Group 2A)	**Epidemiological evidence. Limited** Reported epidemiological evidence is strongest for nasal and nasopharyngeal cancer, noted limitations with small numbers of exposed cases and inconsistent reports. Leukemia: "Excess mortality from leukemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excess for these cancers among professionals is due to conditions other than formaldehyde. The slight excesses of cancer among professionals noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level, or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies."
			Toxicological evidence. Sufficient No changes in information reported from IARC, Suppl 4, 1982
			Supporting data. "In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings (IARC, Suppl 6, 1987)."

Year	Agency	Carcinogenicity Classification	Findings
1991	EPA (EPA, 1991)	Probable human carcinogen (Group B1)	**Epidemiological evidence. Limited** (28 studies considered) "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products." (p.7) Leukemia: "Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated." (p. 8)
			Toxicological evidence. Sufficient, nasal squamous cell carcinomas Increased incidence of nasal squamous cell carcinomas observed in rats and mice in long-term inhalation studies.
			Supporting data. "The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde." (p. 7)
1994 [c]	IARC (Monographs Volume 62, 1995)	Probably carcinogenic to humans (Group 2A)	**Epidemiological evidence. Limited** Lack of consistency between cohort and case-control studies of cancers of the nasal cavities and paranasal sinuses. Leukemia: "The studies of industrial cohorts also showed low or no risk for lymphatic or haematopoietic cancers; however, the cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by a consistent lack of excess risk for brain cancer in the studies of industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists." (p.334)
			Toxicological evidence. Sufficient (nasal squamous cell carcinomas) Squamous cell carcinomas of nasal cavities, at highest exposure. No evidence of carcinogenicity in hamsters. Mice showed no effect or were inadequate for evaluation.
			Supporting data. Genotoxic in variety of experimental systems *in vivo.* Induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, gene mutation in human and rodent cells *in vitro.*

Year	Agency	Carcinogenicity Classification	Findings
2004 [d]	IARC (Monographs Volume 88, 2006)	Carcinogenic to humans (Group 1)	**Epidemiological evidence.** Sufficient, based on nasopharyngeal cancer Leukemia: "There is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers." (p.276)
			Toxicological evidence. Sufficient (nasal squamous cell carcinoma)
			Supporting data. Mechanism for inducing myeloid leukema is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells. "The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukaemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans." (p. 280)
2009 [e]	IARC (Monographs Volume 100F, 2012)	Carcinogenic to humans (Group 1)	**Epidemiological evidence**. Formaldehyde causes cancer of the nasopharynx **and leukaemia**. "The Working Group was not in full agreement on the evaluation of formaldehyde causing leukaemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited." (p. 430)
			Toxicological evidence. "Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427) "Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p.428) Inconsistent genotoxic effects in blood lymphocytes from animals exposed to formaldehyde via inhalation.
			Supporting data. "Particularly relevant to the discussions regarding sufficient evidence was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukeaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological prescursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430) "Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the mechanisms is the most important." (p. 430)

Year	Agency	Carcinogenicity Classification	Findings
2010	EPA (Draft IRIS Toxicological Review, 2010)	Carcinogenic to humans	**Epidemiological evidence.** Sufficient "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (page 6-46). For all LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts (embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (page 4-180). For all leukemias as a group: "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group." (page 4-182)
			Toxicological evidence. Limited evidence to support conclusion that formaldehyde exposure causes leukemia. Four studies evaluated the leukemic potential of formaldehyde. "Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after chronic inhalation exposures (Sellakumar et al., 1985)." (p.6-21)
			Supporting data. "Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been coumented in formaldehyde exposed workers, including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells." (p.6-22)
2012	NTP (12^{th} RoC, 2013)	Known to be a human carcinogen	**Epidemiological evidence.** Causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia." (p. 195)
			Toxicological evidence. No specific evidence cited regarding leukemia beyond the following: "Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased

Year	Agency	Carcinogenicity Classification	Findings
			after long-term exposure of adults; however, it is unclear whether these turmos were exposure-related, because of limitations in the reporting of these tumors (Soffritti et al., 2002)." (p. 198)
			Supporting data. "Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al. 2010a). Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. The endogenous concentration in the blood of humans, monkeys, and rats is about 2 to 3 μg/g, and the concentration does not increase after inhalation of formaldehyde from exogenous sources (Heck et al. 1985, Casanova et al. 1988, Heck and Casanova et al. 2004). Moreover, N2-hydroxymethyl-dG–DNA adducts have not been detected at distal sites in rats (such as the bone marrow, white blood cells, lung, spleen, liver, or thymus) (Lu et al. 2010). For these reasons, the plausibility of formaldehyde's causing cancer at distal sites, such as myeloid leukemia, has been questioned (Golden et al. 2006, Pyatt et al. 2008). However, systemic effects have been observed after inhalation or oral exposure, and although the mechanisms by which formaldehyde causes myeloid leukemia in humans are not known, a number of plausible mechanisms have been advanced. These include (1) theoretical mechanisms for the distribution of formaldehyde to distal sites and (2) proposed mechanisms of leukemogenesis that do not require formaldehyde to reach the bone marrow. In addition, there is some evidence that formaldehyde causes adverse haematological effects in humans." (p. 199)
2012	RAC (RAC, ECHA, 2012)	Carc. 1B - H50 [f] May cause cancer	**Epidemiological evidence.** Limited "In conclusion, while some studies have found increased rates of leukaemia, the epidemiology data do not show consistent findings across studies for leukaemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukaemia rates among embalmers, pathologist and anatomists, but not among industrial workers, suggests the possibility of confounding factors that bear investigation. Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukaemia." (p.41)
			Toxicological evidence. "No indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumours in inhalation study of rats and mice (Kerns et al. 1983)." (p.22)
			Supporting data. "Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found at values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde.

Year	Agency	Carcinogenicity Classification	Findings
			These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the port of entry." (p.44)
2016	Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL, 2016)	Carcinogen Group C (genotoxic carcinogen with a mode-of-action based threshold)	**Epidemiological evidence**. "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45)
			Toxicological Evidence. "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49)
			Supporting Data. "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49)

[a]IARC Working Group met February 1981. IARC Preamble (1982): "For many of the chemicals evaluated in the first 29 volumes of the /ARC Monographs for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer."

[b]IARC Working Group met March 1987.

[c]IARC Working Group met October 1994; monograph published 1995.

[d]IARC Working Group met June 2004; monograph published 2006.

[e]IARC Working Group met October 2009; monograph published 2012.

[f]EU harmonized classification and labelling.

Table 2: Summary of NAS (2011) Comments or Identified Data Gaps and New Formaldehyde Science by Lines of Inquiry

NAS (2011) Comment / Identified Data Gap	New Formaldehyde Science
A. Epidemiological Evidence	
Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). *(NAS, p. 113)*	New analyses of the NCI formaldehyde workers cohort specifically for AML are reported. Results do not support the hypothesis that formaldehyde causes AML. ***Checkoway et al. (2015)*** Associations seen between formaldehyde exposure and Hodgkin lymphoma and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. ***Checkoway et al. (2015)***
Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. *(NAS, p. 113)*	A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoetic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation. ***Checkoway et al. (2012)***
Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. *(NAS, p. 112-113)*	Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure, and few deaths occurred within 20 or more years of last peak exposure. Suggestive associations with peak exposure were observed for chronic myeloid leukemia, based on very small numbers. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (p_{trend}= 0.05) and peak (p_{trend} = 0.003) exposures. However, no other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. ***Checkoway et al. (2015)***
The selection and use of the NCI cohort (Beane-Freeman et al. 2009) should be further justified. *(NAS, p. 112)*	Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941-2012. Results provide no support for an increased hazard of myeloid leukemia from formaldehyde exposure. ***Coggon et al. (2014)***

NAS (2011) Comment / Identified Data Gap	New Formaldehyde Science
	Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results demonstrated limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases. ***Meyers et al. (2013)***
B. Toxicological Evidence	
Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. *(NAS, p. 110)*	No cases of leukemia or lymphohematopoietic neoplasia were seen. FA inhalation did not cause leukemia in genetically predisposed C3B6.129F1-*Trp53*tm1Brd mice. ***Morgan et al. (2014)***
	FA inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. ***Morgan et al. (2015)***
C. Mode of Action Evidence	
Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. *(NAS, p. 58)*	Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations. ***Schroeter et al. (2014)***
	With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. ***Yu et al. (2015)***

NAS (2011) Comment / Identified Data Gap	New Formaldehyde Science
Reconcile divergent statements regarding systemic delivery of formaldehyde *(p.59)*; direct evidence of systemic delivery of formaldehyde is generally lacking. *(NAS, p.5)*	Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. Also, new evidence suggests that endogenous formaldehyde in bone marrow is toxic and carcinogenic, and may cause leukemia (but not exogenous formaldehyde). ***Lai et al. (2016)*** ***Gao et al. (2016)*** ***Yu et al. (2015)*** ***Edrissi et al. (2013)*** ***Moeller et al. (2011)*** ***Lu et al. (2011)***
Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. *(NAS, p. 5)*	Critical review of the genotoxicity literature found no convincing evidence that exogenous exposures to FA alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically not in the bone marrow. Review of the existing studies of hematotoxicity, likewise, failed to demonstrate myelotoxicity in any species– a probable prerequisite for leukemogenesis. ***Albertini and Kaden (2016)***
	Reanalysis of selected raw data from the Zhang et al. (2010) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect in vivo events, the reanalysis of the results provided by Zhang et al. (2010) raise sufficient questions that limit the use of Zhang et al. (2010) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. ***Gentry et al. (2013)***

NAS (2011) Comment / Identified Data Gap	New Formaldehyde Science
	Additional analyses were performed on the study data obtained from the original study (Zhang et al. 2010) including individual average formaldehyde exposure concentration measurements performed for each exposed worker. The objective was to evaluate hematological parameters and aneuploidy in relation to quantitative exposure measures of formaldehyde. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Furthermore, among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk. ***Mundt et al. (2017)***
D. Dose-Response Assessment	
Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. *(NAS, p. 14)*	The documentation of the methods applied in the USEPA (2010) IRIS document lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the *Beane Freeman et al. (2010)*. This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. ***Van Landingham et al. (2016)***
BBDR models developed by Conolly and co-workers should be used. *(p.58)* These models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. (*NAS, p.57)*	Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. ***Clewell et al. (in preparation)***

NAS (2011) Comment / Identified Data Gap	New Formaldehyde Science
Consideration of the use of alternative extrapolation models for the analysis of the cancer data. *(NAS, p.14)*	Results of the "Bottom-up " approach indicate that recent top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. ***Starr and Swenberg (2013)***
	Updated "Bottom-Up" risk estimates heighten the marked contrasts that are present between the previous estimates and the corresponding USEPA estimates, with the larger difference for leukemia being due primarily to the significantly improved detection limit for the analytical method used in quantitating DNA adduct numbers. ***Starr and Swenberg (2016)***
E. Methods for Evidence Integration	
EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. *(NAS, p. 113)*	A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode-of-action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. ***Rhomberg et al. (2011)***

Highlights

- A 2011 NRC report challenged leukemia causation in IRIS Draft Formaldehyde Review
- Studies published since IRIS Draft provide new evidence for evaluating formaldehyde
- Integration of evidence does not support formaldehyde as a cause of leukemia
- Valid hazard classification of formaldehyde has significant regulatory implications

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The need for transparency and reproducibility in documenting values for regulatory decision making and evaluating causality: The example of formaldehyde

Cynthia Van Landingham [a], Kenneth A. Mundt [b], Bruce C. Allen [c], P. Robinan Gentry [a, *]

[a] Ramboll Environ US Corporation, 3001 Armand St., Suite I, Monroe, LA 71201, United States
[b] Ramboll Environ US Corporation, 28 Amity St., Suite 2A, Amherst, MA 01002, United States
[c] Independent Consultant, 101 Corbin Hill Circle, Chapel Hill, NC 27514, United States

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ABSTRACT

Reproducibility and transparency in scientific reporting is paramount to advancing science and providing the foundation required for sound regulation. Recent examples demonstrate that pivotal scientific findings cannot be replicated, due to poor documentation or methodological bias, sparking debate across scientific and regulatory communities. However, there is general agreement that improvements in communicating and documenting research and risk assessment methods are needed. In the case of formaldehyde, the peer-review conducted by a National Academy of Sciences (NAS) Committee questioned the approaches used by the Integrated Risk Information System (IRIS) in developing draft unit risk values. Using the original data from the key study (Beane Freeman et al., 2009) and documentation provided in the draft IRIS profile, we attempted to duplicate the reported inhalation unit risk values and address the NAS Committee's questions regarding application of the appropriate dose-response model. Overall, documentation of the methods lacked sufficient detail to allow for replication of the unit risk estimates, specifically for Hodgkin lymphoma and leukemias, the key systemic endpoints selected by IRIS. The lack of apparent exposure-response relationships for selected endpoints raises the question whether quantitative analyses are appropriate for these endpoints, and if so, how results are to be interpreted.

1. Introduction

Reproducibility and transparency in scientific research and reporting, both in the published literature and in documentation of decisions related to public health reached by authoritative bodies, have received significant discussion and debate (Bustin and Nolan, 2015; Campbell, 2014; Iqbal et al., 2016; Jilka, 2016). The National Institutes of Health (NIH) are exploring ways to provide greater transparency of the data that are the basis for published manuscripts (Collins and Tabak, 2014) and have noted that the greater scientific community must take steps to correct this issue. In addition, recent commentaries and surveys highlight the growing lack of reproducibility in scientific research (Anonymous, 2016). One of the most immediate and impactful consequences for a lack of transparency or reproducibility is in the direct reliance on published but un-replicated scientific findings for human health risk assessment, including the derivation of cancer unit risk estimates.

In 2011, the National Research Council (NRC) of the National Academy of Sciences (NAS) convened a Committee to Review USEPA's Draft of the *Toxicological Review of Formaldehyde – Inhalation Assessment* in support of the Integrated Risk Information System (IRIS) (NRC, 2011). The Committee noted:

> *"Problems with clarity and transparency of the methods appear to be a repeating theme over the years, even though the documents appear to have grown considerably in length"*

A further review of the IRIS process in 2014 (NRC, 2014) noted progress in meeting the NRC (2011) recommendations, but further noted:

* Corresponding author.
E-mail address: rgentry@ramboll.com (P.R. Gentry).

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"However, NRC committees have conducted several reviews of some of the more complex and challenging IRIS assessments in the last decade and have identified methodologic problems and pointed out deficiencies in EPA's approaches."

Formaldehyde provides one such complex database that introduces significant challenges for consideration in a standard IRIS assessment. It is an endogenously generated compound and, for selected endpoints, multiple studies provide inconsistent results, a few of which have suggested associations with formaldehyde exposure. Some have interpreted these findings (generally at face value and apart from the larger body of results) as reflecting causal associations. As an example, there has been much scientific debate regarding whether there is a causal association between formaldehyde exposure and selected lymphohematopoietic (LHP) endpoints, especially acute myeloid leukemia. Multiple authoritative bodies (IARC, 2012; NTP, 2014) have made hazard classification decisions (sufficient evidence in humans, known to be a human carcinogen) based on conclusions that the available evidence is sufficient to conclude that there is a causal association. For the LHP cancers, these conclusions have been based on the grouping of different types of cancers from a limited number of epidemiological studies (Zhang et al., 2009; Beane Freeman et al., 2009), with little or no consideration of findings reported in many other studies or the animal or mechanistic information, much of which lends no support for or even contradicts these conclusions. It is important to note that in reviewing the same critical studies for formaldehyde as IARC (2012) and NTP (2014), the European Chemicals Agency (ECHA, 2011) concluded that

"Altogether, in absence of convincing evidence for a biologically plausible mechanism and considering the discrepancy of results in epidemiological studies, a causal relationship between formaldehyde exposure and induction of myeloid leukaemia cannot be concluded."

The 2010 draft IRIS *Toxicological Review of Formaldehyde – Inhalation Assessment* provided the first quantitative estimates of a dose-response relationship between two lymphohematopoietic endpoints, Hodgkin lymphoma (HL) and all leukemias (combined category), and exposure to formaldehyde based on the results from a single epidemiological study (Beane Freeman et al., 2009). The use of these two endpoints by USEPA (2010) for the estimation of unit risk factors was based on the conclusion that the weight of the epidemiologic evidence supported a link between formaldehyde exposure and LHP cancers, particularly myeloid leukemias. In addition to HL largely being considered unrelated to environmental exposures, no other key epidemiological study demonstrates such an association, raising questions as to the validity of the finding in Beane Freeman et al. (2009). As for the combination of all leukemias, little scientific basis is provided for aggregating what increasingly are understood to be diverse diseases with different etiologies, prognoses and treatments.

In 2011, the NRC Committee review noted many uncertainties in the approach used by USEPA (2010) to estimate risk values. The Committee recognized that USEPA (2010) had relied upon selected associations reported between formaldehyde and various LHP cancers from a single study (Beane Freeman et al., 2009). The NRC (2011) Committee further recommended that USEPA conduct an independent analysis of the dose-response models to confirm the degree to which the models fit the data appropriately, as well as consider the use of alternative extrapolation models for the analysis of the cancer data. The NRC (2011) Committee concluded that this is especially important, given the use of a single study, the inconsistencies in the exposure measures, and the uncertainties associated with the selected cancers. In addition to the impact of these assumptions, the NRC (2011) Committee noted that while the National Cancer Institute (NCI) cohort studies, including Beane Freeman et al. (2009), may be the only studies with sufficient exposure and dose-response data needed for risk estimation, they are not without weaknesses and these need to be considered. This recommendation from the NRC (2011) Committee raised several challenges. While there is some guidance provided for the use of animal data for dose-response modelling (USEPA, 2012), the use of epidemiological data in the estimation of inhalation unit risk (IUR) estimates does not have guidance that provides a "road map" for conducting these types of assessments. When using epidemiological data for the estimation of unit risk values, more extensive documentation in the IRIS profile is needed to be able to clearly understand the data relied upon and the methods applied.

In a separate study (Checkoway et al., 2015), the raw data from the NCI cohort study (Beane Freeman et al., 2009) were obtained through a Technology Transfer Agreement (TTA) with the objective of replicating the findings reported by Beane Freeman et al. (2009), as well as conducting additional analyses not reported by Beane Freeman, specifically, acute myeloid leukemia (AML). The availability of these data provided an opportunity to attempt to replicate the unit risk estimates derived by USEPA (2010), as well as address some of the questions raised by NRC (2011). In addition, it offered the opportunity to conduct alternate independent analyses to evaluate specific leukemias, rather than all leukemias combined, and the impact of alternate dose-response models on the estimates of inhalation unit risk. The methods and results of the attempt to duplicate the USEPA (2010) unit risk values, as well as conduct alternate and independent analyses to address the questions raised by NRC (2011) are reported here.

2. Methods

2.1. Duplication of USEPA (2010) reported unit risks

Our goal was to follow the same process and methods used by USEPA (2010) in the estimation of unit risk factors for the two LHP cancers (Hodgkin Lymphoma and all leukemias (combined category)). However, as noted by NRC (2011), the documentation provided in USEPA (2010) related to the assumptions and processes used in the estimation of the unit risk values was limited. NRC (2011) has outlined five steps that it appears USEPA (2010) used in the estimation of formaldehyde unit risks:

1. Evaluate the association between formaldehyde exposure and LHP endpoints;
2. Convert the relative risk estimates into lifetime risk for the exposed population;
3. Compute lifetime risks for Hodgkin Lymphoma and/or all leukemia for the unexposed population;
4. Determine the maximum likelihood and lower bound estimates of the point of departure; and
5. Estimate inhalation unit risks.

Using these five steps, we attempted to duplicate the USEPA (2010) reported unit risks for Hodgkin lymphoma and "all leukemias" using the raw data from the Beane Freeman et al. (2009) study. In order to conduct this estimate, the following were needed:

- *An estimate of cumulative dose for each individual in the cohort.* This information was not provided in either USEPA (2010) or Beane Freeman et al. (2009) and must be determined from the raw data.

- *Person time at risk for each individual.* Also not provided in USEPA (2010) or Beane Freeman et al. (2009) and must be determined from the raw data.

Absent this necessary information and with no data available to confirm how it was used in estimating risk, assumptions were necessary that impact the estimation of parameters characterizing the relationship between dose and response.

NRC (2011) also recommended that the evaluation of the epidemiological data focus on the most specific diagnoses available. Based on this recommendation, analyses were conducted to include the consideration of individual LHPs rather than combination of endpoints (e.g. all leukemias) and evaluation of alternate dose-response models for these individual endpoints. While the impact of dose metric selection (e.g., 'peak'[1] versus cumulative) has been a point of discussion in interpretation of the NCI cohort (Checkoway et al., 2015), specifically the lack of actual peak measures or estimates, the USEPA (2010) has noted that cumulative exposure is generally the preferred metric for quantitative risk assessment and was relied upon for the estimation of unit risk values. Therefore, the analyses reported below focused on cumulative exposure estimates based on the data obtained through the TTA and reported in Beane Freeman et al. (2009) and Checkoway et al. (2015).

2.2. Evaluation of model selection

NRC (2011) noted that information was needed on the degree to which the model used (i.e., Poisson regression model) fits the data, especially for dose-response analysis. NRC (2011) further noted that this type of analysis is essential because dose-response models for risk estimation must fit the data well in the low-dose range and alternative extrapolation models, including Cox regression models and nonlinear model forms, should be considered in order to identify the best-fitting model. We conducted additional analyses to evaluate the potential impact of NRC (2011) comments on both the methods and the data relied upon for unit risk estimation, as well as consideration of multiple models. In addition to a Poisson regression model, the logistic regression model was considered, as well as a Cox regression model that was applied to the data from Beane Freeman et al. (2009) by Checkoway et al. (2015). All models used a 2-year lag for exposure, which is consistent with a lag considered by both Beane Freeman et al. (2009) and Checkoway et al. (2015).

A log-linear Poisson model, which is the model reported by Beane Freeman et al. (2009) to estimate the exposure-response relationship (β values), was used to compare the results in this analysis to the results published in Beane Freeman et al. (2009) in which the cumulative 2-year lag exposure variable was categorized into discrete exposure variables using the 4 categories reported (0 ppm-years, >0 and < 1.5 ppm-years, ≥1.5 and < 5.5 ppm-years, and ≥5.5 ppm-years). A log-linear Poisson model was also fit using the discrete dose categories reported by Checkoway et al. (2015) (<0.5 ppm-years, ≥0.5 and < 2.5 ppm-years, and ≥2.5 ppm-years). In addition, both a log-linear Poisson model and a logistic regression model were fit to the data using a categorization scheme for the 2-year lag cumulative dose that split the data into quartiles so that an approximately equal number of subjects were in each group (<0.05 ppm-years, ≥ 0.05 and < 0.4 ppm-years, ≥0.4 and < 2.4 ppm-years, and ≥2.4 ppm-years). All models were run considering person-time at risk, sex and race and adjusted for pay type (i.e., hourly vs. salary). For the logistic and Poisson models, quadratic terms for exposure were also considered. For evaluation of potential model fit to the data in the low concentration region, a visual examination of the Poisson and log-logistic model estimates were compared to the case status at the end of follow-up for each individual, again considering person-time at risk, sex, race and pay type.

[1] The 'peak' exposure metric used in Beane Freeman et al. (2009) is a relative peak estimator described in Stewart et al., 1986.

3. Results

3.1. Duplication of USEPA (2010) reported unit risks

3.1.1. Step 1 – evaluate the association between formaldehyde exposure and LHP endpoints

The attempt to estimate the unit risks reported in USEPA (2010) was initiated using the model parameters (β parameters from the log-linear Poisson regression model) provided to USEPA via personal communication by Dr. Laura Beane Freeman. The β parameters describe the relationship between exposure and response. Prior to estimating the unit risk, using the raw data, we attempted to replicate the model parameter estimates provided to the USEPA (2010) by Dr. Beane Freeman using log-linear Poisson regression, which is the same modelling approach reported to have been used to develop these estimates in both the Beane Freeman et al. (2009) publication and in the draft IRIS evaluation (USEPA, 2010) (Table 1). In addition, Cox and logistic regression models were considered.

Since cumulative exposure was the focus of the USEPA (2010) unit risk estimates, an initial analysis to evaluate the association between this exposure metric and the two endpoints relied upon for unit risk estimates (i.e., Hodgkin lymphoma and all leukemias combined) was conducted. Several variables were needed from the raw data, including the estimate of cumulative exposure (ppm) for each individual and person time at risk for each individual, neither of which are provided in USEPA (2010) or Beane Freeman et al. (2009) and had to be estimated from the raw data. In addition, in order to estimate the β parameters, the raw data regarding the number of deaths from a specific cancer and corresponding exposure metric must be divided into the same exposure quartiles as those reported by Beane Freeman et al. (2009) to evaluate the exposure-response relationship.

For the current analyses, the following steps were conducted to identify the data needed for analysis.

1. Using the work history data and date of birth, the data records were combined and organized to result in one or more record for each job so that no record spanned a calendar year or a change in age. Calculation of the duration of each work record was performed in this step with consideration of leap years. Since only start and stop months of work were provided in the raw data from Beane Freeman et al. (2009), the initial start and final stop day for a job were assumed to be the 15th of the month unless the start and stop months were the same month in the same year. In this case, the stop day was assumed to be the appropriate value for the end of the month (28, 29, 30 or 31). The gender, race, salary code and status of each individual (alive or dead) and cause of death ICD code were also attached to the individual's record.
2. The exposure and duration of exposure were summed over the months in a year when the individual was a specific age. During this step, the peak exposure category for each work record was determined.
3. The cumulative and lagged cumulative exposure and person-years of exposure were calculated.
4. The records were categorized into the strata of ranges of years (groups covering a 5 year period starting with 1960 and ending

Table 1
Comparison of modelling statistics from the current analysis to statistics reported in USEPA (2010).

	Current analysis												USEPA (2010)		
	Cox regression			Logistic regression					Poisson regression						
	p-value [a]	β (per ppm x year)	Standard error (per ppm x year)	R^2	LR p-value[b]	p-value [a]	β (per ppm × year)	Standard error (per ppm × year)	LR p-value[b]	p-value [a]	β (per ppm × year)	Standard error (per ppm × year)	p-value	β (per ppm × year)	Standard error (per ppm × year)
Hodgkin lymphoma (201)	0.013	0.0294	0.0119	0.0133	0.098	0.019	0.0288	0.0123	0.09	0.037	0.0243	0.0117		0.02959	0.01307
Leukemia (204–207)	0.058	0.0117	0.0062	0.0017	0.35	0.055	0.0121	0.00628	0.003	<0.001	0.0206	0.0057	0.08	0.01246	0.000642
Leukemia (204–207, excluding 204.1)	0.239	0.0092	0.0079	0.0011	0.64	0.206	0.01	0.00791	0.034	0.013	0.018	0.0073	–	–	–
Acute myeloid leukemia (205.0)	0.844	−0.004	0.0201	0.0016	0.82	0.869	−0.0032	0.0196	0.81	0.80	0.0045	0.0179	–	–	–

Cox regression model $h(t,x) = h_0(t)\ exp(\beta x + \gamma z)$.
Logistic regression model $Y = 1/[1 + exp(-\alpha + \beta x + \gamma z)]$.
Poisson regression model $Ln(Y/t) = \alpha + \beta x + \gamma z$ OR $Y = t\ exp(\alpha) \times exp(\beta x)) \times exp(\gamma z)$.
Where Y is the expected number of events, α is the intercept, β is the slope term, x is the exposure, z is a covariate and t is the duration of exposure. In the Cox model h is the hazard rate.

[a] These p-values reflect the precision of any association between exposure and response, and show the probability that the beta value is not significantly different from zero. P-values < 0.5 indicate that the beta parameter is significantly different from zero.

[b] The likelihood ratio p-values of difference between a null and dose-dependent model (e.g. test of β = 0) where small p-values reject the hypothesis that β = 0.

with 2010), and age groups (groups covering a 5 year range starting with the age of 15 and ending with 85), where the lowest year group included all records prior to 1965, and the 1965 group included years 1965 through 1969, with all job records occurring in 2010 and after included in the 2010 category. For ages, all ages less than 20 were included with the 15 year old age group, and the second group labelled 20 included all ages from 20 through 29.

5. The final record for each individual included an indication of dead or alive. For those individuals who had died, the ICD codes were used to set up yes/no flags indicating whether Hodgkin lymphoma, leukemia or acute mylogenous leukemia were found in that individual.

This process resulted in 1,047,291 work records that were then used in the analyses. All analyses used stratification for age group, year group, gender and race, with all the models adjusted for salary type treated as a classification variable. The Poisson analysis (SAS Proc Genmod) used a Poisson distribution, a log link and an offset of the natural log of the cumulative person-years of exposure. SAS Proc Logistic was used to perform the logistic regression and Cox proportions hazards models were performed using STATA (Checkoway et al., 2015).

Beane Freeman et al. (2009) reported that the cut points for the exposure groups were based on the approximate 60th and 80th percentiles from the cumulative exposures for those subjects with cancer. In attempting to duplicate the number of cancers within each exposure group, the cut points of 1.5 and 5.5 ppm-years (cumulative exposure groups defined by Beane Freeman et al. (2009) as ≤0 to 1.5, 1.5 to <5.5, ≥5.5 ppm-years) could not be duplicated based on the estimated 60th and 80th percentiles using the raw data. The calculations for the current assessment resulted in the determination of 1.2 and 4.2 ppm-years as the 60th and 80th percentiles for the cumulative exposure of the subjects with cancer. In addition, the number of unexposed workers (4359) reported by Beane Freeman et al. (2009) could not be replicated. Using the raw data, only 2676 unexposed workers could be identified.[3]

Regardless of the lack of ability to duplicate this determination of exposure, an evaluation of the exposure-response relationship was conducted. For the "all leukemia" category, exposure-response was evaluated including and excluding chronic lymphocytic leukemia (CLL), because, as noted by Checkoway et al. (2015), CLL has been classified as a non-Hodgkin lymphoma (NHL) since 2001 (Muller-Hermelink et al., 2001; Campo et al., 2011).

Other models were attempted in this process. Using quadratic terms for exposure failed to provide any better fit of the models to the data. In addition, the effect of exposure to other substances were explored but these did not improve the model fits substantially, either.

As noted in Table 1, in attempting to duplicate the β parameter and standard error for each cancer type, similar values could be estimated, but the estimates reported in USEPA (2010) could not be duplicated, which can impact attempting to duplicate unit risk estimates. In addition, it is important to note that no significant association between leukemia as a class of diseases (p-values > 0.05; Table 1) or specifically for acute myeloid leukemia ($p \geq 0.8$) with cumulative exposure to formaldehyde was found (using the typical 0.05 as the determinant of "significant") for either the Cox regression or the logistic regression. In addition, the estimated β parameter for acute myeloid leukemia (~-0.004 from the Cox regression and the logistic regression) indicates that the slope is in the negative direction (decreasing incidence with increasing exposure). These results for AML suggest that it would not be appropriate to rely upon these negative data independently in the dose-response modelling for the estimation of a unit "protection" estimate. As imprecise positive estimates of a β parameter should not be interpreted as evidence of risk, imprecise negative β parameters should not be interpreted as beneficial or protective. For all the logistic models, the likelihood ratio test indicates that the β parameter is not statistically different from zero. Similarly the likelihood ratio test of the Poisson models for Hodgkin lymphoma and the acute myeloid leukemia also indicate that the β parameter is not statistically different from zero. Only for the Poisson models of combined leukemias are the β values considered to be statistically significantly different from zero. However, as these are

combined types of leukemia which are not recommended by the NRC (2011) and there is almost a factor of 2 difference between the β estimates between the different models in the current analysis and the USEPA (2010) β estimate, there is still large uncertainty in the results.

The estimated β parameter for Hodgkin lymphoma was comparable to that reported in USEPA (2010); however, there was a difference in the standard error and a larger difference in the p-values. USEPA (2010) reported a non-significant trend between cumulative formaldehyde exposure and Hodgkin lymphoma based on information reported in Beane Freeman et al. (2009), while the current analysis suggested a significant trend (p-value = 0.013). These results are consistent with those reported by Checkoway et al. (2015). However, Checkoway et al. (2015) notes that the increased risk of HL has not been observed in other occupational studies of formaldehyde-exposed cohorts, and is not regarded as plausibly related to environmental chemical exposures.

Because the β parameters could not be duplicated, it was concluded that while additional steps could be conducted to evaluate the transparency of the process, the lack of ability to duplicate this first step would result in a lack of ability to duplicate the reported unit risks. Even having access to the raw data from the Beane Freeman et al. (2009) study, there were not enough details regarding the methods used to evaluate the data provided in USEPA (2010) to duplicate the initial β parameters necessary to initiate the unit risk estimate process.

3.1.2. Step 2 – convert the relative risk estimates into lifetime risk for the exposed population

Relying strictly on the β parameters reported in USEPA (2010), even though they could not be duplicated, an attempt was made to conduct the remaining steps of the estimation of unit risk as outlined by NRC (2011). USEPA (2010) noted that the β parameters were used in a life table analysis to calculate lifetime extra cancer risks from formaldehyde exposure. This step, as well as step 3, requires the use of a life-table method in conjunction with (a) the Poisson model mortality risk, (b) age-specific all-cause mortality rate in the United States population, and (c) Hodgkin lymphoma and all leukemia mortality rates, all of which can be derived from the NCI's Surveillance, Epidemiology and End Results (SEER) database. SEER collects cancer incidence data from multiple geographical areas in the United States. This step also requires estimates of the effective concentration (EC) for occupational exposure adjusted to continuous ambient exposure (the standard exposure metric relied upon by USEPA in the estimation of a unit risk) by multiplying by the ratio of days in a year to work days (240, 50 weeks of 5 day work weeks) and the ratio of daily inhalation rate (20 m^3) to work day inhalation rate (10 m^3) (USEPA, 2010).

$$EC = exposure\ (ppm) \times \frac{365}{240} \times \frac{20}{10}$$

USEPA (2010) provided a spreadsheet (Appendix C of USEPA, 2010; Supplemental Tables S1 and S2) illustrating the life table used for the extra risk calculation for the derivation of the LEC_{0005} (95% lower confidence limit on the effective concentration corresponding to an extra risk of 0.05%) relied upon for estimating the IUR based on nasopharyngeal (NPC) mortality reported by Hauptmann et al. (2004). USEPA (2010) noted that the same general methodology described for NPC mortality estimates was used for Hodgkin lymphoma and leukemias, with the following exceptions:

- U.S. age-specific 2006 all-cause mortality rates (NCHS, 2009);
- NCHS age-specific 2002–2006 background mortality rates for Hodgkin lymphoma and leukemia (http://seer.cancer.gov/csr/1975-2006/) for all race and gender groups; and
- A 2-year lag period instead of a 15-year lag period.

It is important to note that USEPA (2010) provided no citation for the NCHS (2009) all-cause mortality rates, so it was assumed this was obtained from the NCHS website (http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf) as the background mortality rates for specific cancers (Heron et al., 2006). While this does provide data needed to allow the assessor to attempt to duplicate this procedure, there is no comparable life-table for Hodgkin lymphoma or all leukemias to ensure that comparable results are achieved. Relying upon these sources and following these approaches, the IURs provided in USEPA (2010) could not be duplicated using the reported sources and methodology. This was also true for NPC for which the life table was provided (Appendix C; USEPA (2010)). In attempting to duplicate the IURs reported for NPC, it was determined that the values reported from the use of the life table instructions provided could not produce the reported IURs for NPC (see supplemental Table S1 for the re-creation of the calculations that would correspond to the unit risks reported in USEPA (2010) when using the instructions provided by USEPA (2010) for Table C-1. The difficulty in duplicating the life table reported was related to the function reported for estimating the NPC incidence hazard rate (Column L in Supplemental Table 2). Using the USEPA (2010) β of 0.0518 (SE 0.01915) and the calculations as specified in Table C-1 of USEPA (2010), the estimated EC_{0005} and LEC_{0005} would be 0.103 and 0.0623 ppm, respectively, with a unit risk of 8×10^{-3}. However, the calculations specified in Appendix C of USEPA (2010) indicated a function for the hazard incidence rate of $hx_i = h_i \times (1 + \beta \times xdose)$ which is inconsistent with the model of risk that was used to determine the β value ($RR = e^{\beta X}$, where β represents the regression coefficient for exposure and X is exposure as a continuous variable) (USEPA, 2010). When the hazard rate function is changed to $hx_i = h_i \times (e^{\beta \times xdose})$ to properly reflect the underlying risk function, the values estimated by the revised life table were the same as those reported by the USEPA in Tables 5–11 for EC_{0005} and LEC_{0005} based on NPC incidence for formaldehyde exposure (0.074 and 0.046 ppm, respectively, see supplemental Table S3 for the adjusted life-table calculation). However, it is important to note that these estimates rely upon the β parameters reported in USEPA (2010), which cannot be duplicated.

3.1.3. Step 3 – compute lifetime risks for Hodgkin Lymphoma and/or all leukemia for the unexposed population

As noted in USEPA (2010), USEPA cancer risk estimates are typically derived to represent a plausible upper bound on increased risk of cancer *incidence*, typically based on experimental animal incidence data. However, epidemiological studies more often present results based on mortality data, which is true for the Beane Freeman et al. (2009) study. For cancers with low survival rates, mortality-based estimates are a reasonable approximation of cancer incidence risk. However, USEPA (2010) largely documents its approach to the evaluation of nasopharyngeal cancers and noted the need to estimate incidence-based risks. Estimation of the incidence of a particular cancer type using mortality data can be conducted by acquiring the age-specific incidence rates for a specific cancer from the SEER program. In order to estimate the potential risk of incidence of a cancer type, the data from the SEER database are used to adjust the mortality data assuming that the exposure-response relationship for incidence and mortality of a cancer type are the same. An examination of the assumptions and adjustments made to the Beane Freeman et al. (2009) data for lymphohematopoietic cancers follows.

Table 2
Extra risk estimates for Hodgkin lymphoma mortality from various levels of continuous exposure to formaldehyde (reproduced from Tables 5–14 in USEPA (2010)).

Exposure concentration (ppm)	As reported by USEPA (2010)		Estimated using the life table provided in USEPA (2010) [a] with adjustments to the hazard function	
	Extra risk	95% UCL on extra risk	Extra risk	95% UCL on extra risk
0.0001	2.04×10^{-7}	3.53×10^{-7}	2.52×10^{-7}	4.36×10^{-7}
0.001	2.05×10^{-6}	3.55×10^{-6}	2.53×10^{-6}	4.38×10^{-6}
0.01	2.10×10^{-5}	3.71×10^{-5}	2.59×10^{-5}	4.59×10^{-5}
0.1	2.79×10^{-4}	6.17×10^{-4}	3.44×10^{-4}	7.63×10^{-4}
1	1.63×10^{-1}	8.36×10^{-1}	1.90×10^{-1}	8.53×10^{-1}
10	9.89×10^{-1}	9.90×10^{-1}	9.89×10^{-1}	9.90×10^{-1}

[a] Using the supplied information in the life table provided in USEPA (2010) with an adjustment in column L for the incidence hazard rate in interval I ($hxi = hi \times e^{(\beta \times xdose)}$) for the estimates of $\beta = 0.02959$, SE = 0.01307.

Table 3
Extra risk estimates for leukemia mortality from various levels of continuous exposure to formaldehyde (reproduced from Tables 5–15 in USEPA (2010)).

Exposure concentration (ppm)	Calculated by USEPA (2010)		Estimated using the life table provided in USEPA (2010) [a] with adjustments to the hazard function	
	Extra risk	95% UCL on extra risk	Extra risk	95% UCL on extra risk
0.0001	1.64×10^{-6}	3.02×10^{-6}	1.65×10^{-6}	3.06×10^{-6}
0.001	1.64×10^{-5}	3.03×10^{-5}	1.65×10^{-5}	3.07×10^{-5}
0.01	1.66×10^{-4}	3.10×10^{-4}	1.67×10^{-4}	3.13×10^{-4}
0.1	1.87×10^{-3}	3.90×10^{-3}	1.89×10^{-3}	3.95×10^{-3}
1	8.07×10^{-2}	5.19×10^{-1}	8.16×10^{-2}	5.28×10^{-1}
10	9.80×10^{-1}	9.89×10^{-1}	9.80×10^{-1}	9.89×10^{-1}

[a] Using US 2006 mortality rates, the adjusted life table structure and potency estimates ($\beta = 0.01246$, SE = 0.006421) from USEPA (2010).

Table 4
Relative risk based on peak exposure from Poisson model stratified by calendar year, age, sex and race and adjusted for pay category.

	0 ppm		>0 to <2.0 ppm		> = 2.0 to <4.0 ppm		> = 4.0 ppm		Log likelihood	p-value
Total in group	3139		10,302		6010		6168			
Person-years	104,386		415,987		254,723		256,618			
	Cases	RR (95% CI)	Cases	RR (referent)	Cases	RR (95% CI)	Cases	RR (95% CI)		
Hodgkin lymphoma (201)	2	3.32 (0.60–18.26)	6	1.0	8	0.76 (0.30–1.89)	11	2.96 (0.94–9.27)	−309.87	0.04
Leukemia (204–207)	7	1.83 (0.76–4.40)	41	1.0	27	0.58 (0.36–0.93)	48	0.58 (0.36–0.93)	−1177.94	0.004
Leukemia (204–207, excluding 204.1)	6	1.61 (0.61–4.24)	28	1.0	20	0.56 (0.32–0.96)	37	1.17 (0.65–2.09)	−901.65	0.009
Acute myeloid leukemia (205.0)	4	1.21 (0.33–4.43)	9	1.0	9	0.77 (0.32–1.84)	12	1.72 (0.67–4.43)	−374.47	0.34

Since USEPA's life table analysis relied upon background mortality rates to determine the extra risk from the incidence of the endpoint of interest, the effect of using background incidence data for Hodgkin lymphoma and all leukemia was explored. The background mortality rates were adjusted to reflect the background incidence of the endpoint by replacing the mortality rate attributed

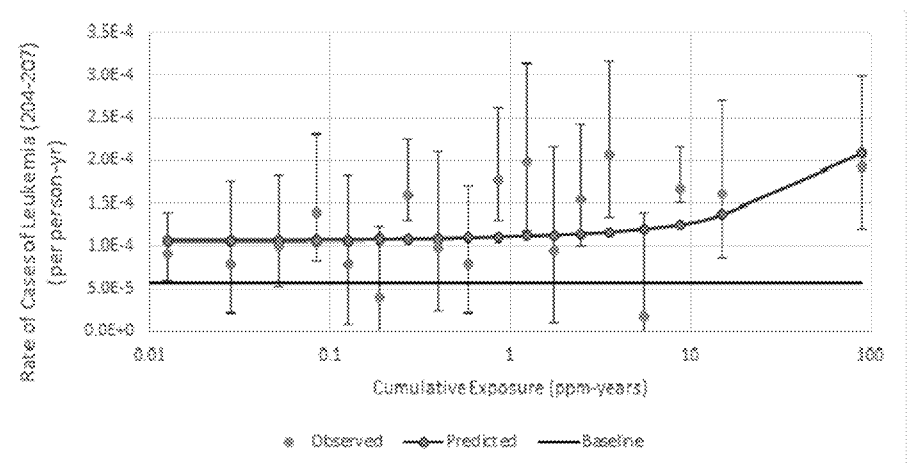

Fig. 1. Comparison of estimated cases from the Poisson regression model to number of cases of leukemia observed at the end of follow-up period in the Beane Freeman et al. (2009) study. Observed and predicted results over full observed exposure range.

to that endpoint with the incidence rate of that endpoint. Making this correction resulted in a difference of between 10 and 21% in the estimated risks for the current analysis.

3.1.4. Step 4 – determine maximum likelihood and lower bound estimates of point of departure

USEPA's carcinogenicity risk-assessment guidelines (USEPA, 2005) recommend the use of an extra risk of 1–10% for deriving effective concentration at the Point of Departure (POD), or for the USEPA (2010) IRIS assessment. NRC (2011) noted that in USEPA (2010) there was an unusual choice of a 0.05% extra risk for Hodgkin lymphoma and 0.5% extra risk for all leukemias. USEPA (2010) noted the issues with using standard extra risk levels (e.g., 10%) in that the risks using these standard extra risk assumptions resulted in relative risk estimates that were substantially higher than those observed in the epidemiology study. Therefore, the choice of the extra risk value to use was based on the background mortality rate for each individual cancer type compared to the relative risk estimates observed in the Beane Freeman et al. (2009) study. Relative risk estimates were determined starting at the 10% extra risk level, decreasing the extra risk level until the relative risk estimates were within the observable range of the epidemiology study. For example, if the 1% level of risk associated with the relative risk estimates for NPC were higher than those observed in the Beane Freeman et al. (2009) study, the extra risk level of concern was lowered until the relative risk estimates were below the relative risk estimates from the Beane Freeman et al. (2009), so an upward extrapolation could be conducted. This approach effectively assumes that nothing observed in the Beane Freeman et al. (2009) could be attributable to background incidence of these cancer types.

Using the hazard rate function as instructed in the life table example (Footnote for Column L, Table C-1 of USEPA (2010)), the extra risk and 95% upper confidence limits on extra risk provided in USEPA (2010) cannot be reproduced (Tables 2 and 3). However, using a life table that had a hazard rate function consistent with the underlying risk function produced results that were similar to those reported by the USEPA (2010). Supplemental Tables S2 and S4 show the differences in the risk values calculated at an exposure of 1 ppm using the USEPA (2010) instructions (Table S2) versus the revised life table (Table S4) with the modified hazard function that was necessary to duplicate the EC, LEC and unit risk values reported in USEPA (2010). While there was some correspondence, there were still some differences in the values that were calculated for the extra risk (Tables 2 and 3) and there is some concern about the appropriateness of the risk estimates, especially large estimates of risk for values above 0.1 ppm. An exposure of 0.1 ppm is within the range of exposures (0.01–4.3 ppm – TWA) reported by Beane Freeman et al. (2009). The relative risk values estimated for these exposures approach 100% and are inconsistent with the observed incidences of cancers in the Beane Freeman et al. (2009) study.

3.1.5. Step 5 – convert the relative risk estimates into lifetime risk for the exposed population

With the results from step 4, the lower bounds on exposure (LECx) and the extra risk level should then be used to determine the unit risks. However, because the model parameters from step 1 could not be replicated, an attempt was made to replicate the MLE and lower bounds using the USEPA (2010) reported model parameters. Using a life table analysis that follows the methods provided in Appendix C of USEPA (2010) and the reported model parameters, the MLE and lower bounds on dose for Hodgkin lymphoma and all leukemia could not be replicated. Using the available parameters and results reported in USEPA (2010) and using the USEPA's parameters, a 12–27% difference in unit risk values was determined for leukemia, Hodgkin's lymphoma and NPC from those reported by the USEPA (2010). However, when the life table was adjusted to be consistent with the relative risk model that was the basis of the β value used in USEPA (2010), the values reported by the USEPA could be replicated.

In noting the potential differences in unit risk estimation, this 12–27% difference could be considered in combination with the potential differences in unit risk from step 1 (differences in the model results), as well as the potential impact of the differences in risk from step 3. Therefore, the inability to replicate individual steps in the process may result in unit risk estimates different from those in USEPA (2010) by 100% or greater due to differences in the slope factors (up to 100% difference) as well as differences in life table analysis results (12–27%) that would be calculated following the documentation provided in USEPA (2010).

Analyses were also conducted using the "peak" exposure metric, rather than the continuous metric relied upon by USEPA (2010) for their evaluation. This was conducted using the same model (log-linear Poisson stratified by calendar year, age sex, and race and adjusted for pay category) as Beane Freeman et al. (2009), but in contrast to the results reported by Beane Freeman et al. (2009), no significant relative risks were estimated (Table 4). Reasons for the differences between the current analyses and those reported by Beane Freeman et al. (2009) could include that the specific dates of job start and job end were not provided, nor were the specific dates that follow-up started or ended: only month and year were reported.

3.1.6. Evaluation of model selection

In evaluating the potential fit of the model to the data, there are various tests that can be performed to look at the predictive power of a model (e.g. R^2 tests, χ^2 tests), to make comparison between models (e.g. AIC and other log-likelihood tests) or graphical representations of the data to visualize the fit. However, since no such statistics were provided in either Beane Freeman et al. (2009) or USEPA (2010), comparisons can only be made among the models fit to the data in this current analysis. The R^2 values reported for the logistic regression performed in this analysis were uniformly poor (i.e., 0.05 or less) indicating poor predictive ability of the models. For the Poisson models, there were small values for the Pearson χ^2 value which, with the large sample size, achieved a better fit to the data (p-values close to 1). However, in graphs presented in this analysis using the data at the end of follow-up, the rate of all leukemias was plotted against the continuous exposure as well as the model predicted rates estimated for both the Poisson regression model (Fig. 1) and the logistic model (Fig. 2).[2] These figures show large variability in the observed rates in the low concentration region which subsequently makes comparison and evaluation of the fit of the model to the data difficult. This variability also makes any predictions made with models fit to these data highly uncertain. In addition, the predictions of extra risk provided by USEPA (2010)

[2] The graphs were constructed using the 5% percentiles (e.g. 5%, 10%, 15%, etc.) of the cumulative exposure, and sums of the person-years, number of individuals and number of observed and predicted leukemias per percentile to determine the rates. The confidence limits for the logistic graph were calculated using binomial confidence limits on the observed rates of leukemia per percentile group of exposure, and the Poisson confidence limits are exact confidence limits based on the Poisson distribution.

[3] This number of unexposed workers identified in the current analysis (2676) is consistent with the number determined by Checkoway et al. (2015) in a separate reanalysis of the raw data from Beane Freeman et al. (2009) study. When this difference was discovered by Checkoway et al. (2015), communications with Dr. Beane Freeman indicated that the number of unexposed workers reported was a mistake and should have been 3,108. However, Checkoway et al. (2015) could not duplicate this number of unexposed workers either using the raw data.

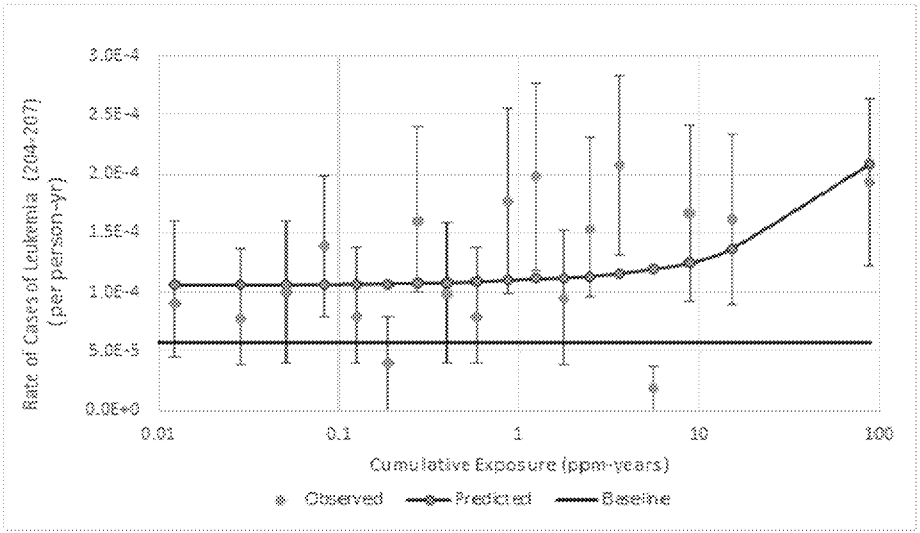

Fig. 2. Comparison of estimated cases from the logistic regression model to number of cases of leukemia observed at the end of follow-up period in the Beane Freeman et al. (2009) study. Observed and predicted results over full observed exposure range.

associated with higher concentrations (1 and 10 ppm) are above the observable range and involve upward extrapolation. The results are estimates of extra risk approaching 1, which are unreasonable.

While each model provides predictions that "run through the middle" of the data, it is clear that neither model can adequately predict the exposure-response relationships or lack of pattern in the lower concentration region (Figs. 1 and 2), as the data in this region of the exposure-response curve appears to be comparable to random variation. In the low concentration region, the data lack a clear monotonic dose-response relationship, which may explain lack of a significant trend ($p = 0.08$) even for the combination of all leukemias. Overall, the models do not fit the pattern of exposure-response in the data. While the models appear to be more consistent with the data at concentrations greater than 10 ppm-years, this comparison is largely influenced by two data points. It is possible that this shape of the exposure-response curve may explain the unusual nonlinearities in the estimates of extra risk provided by USEPA (2010) (Tables 2 and 3). However, explaining this unusual exposure-response behavior is difficult due to the inability to duplicate the unit risk estimates provided in USEPA (2010).

4. Discussion

One of the greatest challenges in attempting to duplicate unit risk factors estimated by USEPA is attempting to duplicate those specifically based on epidemiological data. When USEPA has relied upon animal data for the estimation of unit risk values, even when the documentation provided is limited, there are guidelines available (USEPA, 2012) that provide specific steps and assumptions used by USEPA in the dose-response analysis of animal data. However, when epidemiological data are applied, there is not comparable guidance, and the necessary additional detail may not be provided in the IRIS documentation to allow for transparency and the ability to duplicate risk values.

In the case of formaldehyde, the draft IRIS toxicological review (USEPA, 2010) provided documentation largely on the estimation of IURs from the cases of NPC from the NCI cohort reported by Hauptmann et al. (2004), assuming that these methods could easily be extended in an attempt to duplicate values for lymphohematopoietic cancers provided in an update to the NCI cohort by Beane Freeman et al. (2009). The results from this assessment, in attempting to duplicate unit risk values for lymphohematopoietic cancers, demonstrate that this is not the case.

Difficulty in duplication of results from each step of the process of the estimates of IURs, following the steps as outlined by NRC (2011), started with the initial step that involved duplication of the β parameters from the log-linear Poisson regression model as provided by Dr. Laura Beane Freeman to the USEPA. In the initial step of the process, our results suggest no significant association between cumulative exposure to formaldehyde, which is the exposure metric relied upon by USEPA (2010) for the estimation of the IURs, and either all leukemias combined or acute myeloid leukemia specifically. This lack of association is directly relevant to evaluation of causality and should be considered earlier in the determination of what endpoints likely are caused by exposure to formaldehyde and therefore which associations might be relied upon for the estimation of IURs. Based on the results for all leukemias, as well as AML, with no significant trends observed, it is not appropriate to conduct dose-response modelling only on null findings. In addition, while similar, the β values could not be duplicated even with the availability of the raw data, which suggests that the methods applied are not adequately documented in USEPA (2010).

USEPA (2010) relied heavily upon the Beane Freeman et al. (2009) study for risk estimation associated with lymphohematopoietic tumors, with the NRC (2011) committee noting that this may be the only study with sufficient exposure and dose-response data needed for risk estimation. However, they also noted that this study is not without weaknesses and these need to be considered. A reanalysis of the raw data from the NCI study (Beane Freeman et al., 2009) was conducted by Checkoway et al. (2015). While basic results were replicated, additional analyses of the associations of specific lymphohematopoietic cancers, specifically acute myeloid leukemia (AML) with various metrics of formaldehyde exposure (peak, average, cumulative) and using a more standard definition of peak exposure than that relied on by Beane Freeman et al. (2009) were reported. The re-evaluation highlighted many of the limitations in the data from this cohort, and the new analyses indicated no clear association with AML. It is not clear why AML results had not been reported in any of the updates of this study, and not considered in the IRIS evaluation, given that AML has been highlighted as the lymphohematopoietic cancer most likely to be

relevant to a chemical agent, primarily based on its association with benzene.

The results from the current analysis for Hodgkin lymphoma also provide estimates inconsistent with those reported by USEPA (2010). Using the cumulative exposure metric, USEPA (2010) reported no significant trend for Hodgkin lymphoma. The current analysis suggests a significant trend (Table 1 – p = 0.013), which is consistent with the results from Checkoway et al. (2015) reporting increased relative risk estimates for Hodgkin lymphoma in the highest exposure categories of cumulative and peak exposures. As noted in Checkoway et al. (2015), these findings are complicated because there is little epidemiological support for chemical exposures in the etiology of Hodgkin's lymphoma. There is an absence of an increased risk for this cancer type in other occupational cohorts, as well as the lack of a plausible biological mechanism. In addition, NTP (2014) noted that because the evidence for Hodgkin lymphoma is mainly limited to the NCI cohort study, a causal association is not established. As with all leukemias, including AML, there are questions related to a causal association between cumulative formaldehyde exposure and this cancer type that suggest that the estimation of a quantitative measure of risk using these data are inappropriate.

NRC (2011) also highlighted that the modes of action for formaldehyde-induced Hodgkin lymphoma and for leukemias have not been established. Moreover, the studies that demonstrate the lack of systemic delivery of formaldehyde following inhalation exposure (Lu et al., 2011; Moeller et al., 2011; Edrissi et al., 2013; Yu et al., 2015) draw into question the biological plausibility of formaldehyde causing any LHP cancer. NRC (2011) noted that

> *"Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures."*

Thus, substantial uncertainties remain in using both Hodgkin lymphoma and leukemias (all or individual) for consensus cancer risk estimation. Formaldehyde is rapidly metabolized and highly reactive and, because it is an endogenous compound, a detectable change in the natural background or endogenous levels would need to occur in order to result in the potential for adverse effects. Multiple studies using multiple species, including non-human primates, have been conducted using a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts (Yu et al., 2015; Edrissi et al., 2013; Moeller et al., 2011; Lu et al., 2011). The results of these studies indicated that inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. These results suggest a lack of an ability for exogenous or inhaled formaldehyde exposure to affect endogenously present concentrations of formaldehyde.

Although the Draft Review cites hypotheses proposed by Zhang et al. (2010) regarding the theoretical development of leukemia following inhalation of formaldehyde, there is no documented evidence to support the validity of these hypotheses. In fact, Zhang et al. (2010) note that their hypotheses related to mechanisms of leukemia clearly require additional testing. The existing mechanistic data for formaldehyde provide no evidence that exogenous formaldehyde will be transported from the point of contact to distant sites, but do provide evidence that formaldehyde does not affect the relevant target cells for leukemia (bone marrow or peripheral blood) (Yu et al., 2015; Edrissi et al., 2013; Moeller et al., 2011; Lu et al., 2011).

Overall, the documentation of the methods applied by USEPA lacks sufficient transparency and detail for duplication of the unit risk estimates provided in USEPA (2010), even with the availability of the raw data from the Beane Freeman et al. (2009) study that USEPA relied upon for estimation of the risk of Hodgkin lymphoma or all leukemias. This lack of transparency and detail may result in different estimates of unit risks, including invalid estimates, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints.

In attempting to duplicate the USEPA (2010) calculations, difficulties were encountered at each step, largely due to a lack of critical information provided in the IRIS documentation. Even though analyses were conducted multiple times with different assumptions, all of which could be consistent with the description provided by USEPA (2010), the unit risk values could not be duplicated. The results of the analyses yielded conflicting and different estimates with each step of the analysis, with differences in each step up to a factor of 2. The inability to replicate individual steps in the process may result in unit risk estimates different from those in USEPA (2010) by 100% or greater due to differences in the slope factors (up to 100% difference) as well as differences in life table analysis results (12–27%). Perhaps most problematic, the first step of the analysis did not determine significant exposure-response relationships between formaldehyde and LHP endpoints for the metric (cumulative exposure) needed in the estimation of an IUR. The resulting analysis, while it can be mechanically performed, provides no valid or useful insights on the risks of formaldehyde exposure. Regulatory dependence on these analyses may therefore lead to erroneous guidance, policies and laws.

These results highlight the necessity of clear and transparent reporting of both methods and data used in the estimation of unit risk values. Values provided by the IRIS program of USEPA are relied upon by other federal and state agencies in regulatory decision-making related to the development of standards and guidelines for environmental, consumer product and workplace exposure to chemicals. The inability to duplicate these types of values only escalates the scientific debate over the applicability of these standards and the scientific data necessary to support conclusions regarding acceptable levels of human exposure to chemicals.

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Most of the authors (Gentry, Van Landingham, and Mundt) are employees of Ramboll Environ US Corporation, and performed this work as part of their normal employment. Ramboll Environ US Corporation is a consulting firm providing services in environmental and health sciences matters to private firms, trade organizations, and government agencies. Mr. Allen provided senior technical review on the manuscript and its content as an independent consultant with fee for service. The authors had sole responsibility for the analyses performed, the interpretations made, conclusions drawn and the writing of the paper, which may not necessarily reflect the views of RFHEE. None of the authors have appeared as experts in any litigation related to formaldehyde.

Appendix A.. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2016.10.011.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2016.10.011.

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The University of North Carolina and the American Chemistry Council Collaborated to Organize a Workshop

FORMALEHYDE SCIENCE INVITED EXPERTS WORKSHOP
UNDERSTANDING POTENTIAL HUMAN HEALTH CANCER RISK – FROM DATA INTEGRATION TO RISK EVALUATION
October 10 – 11, 2017
Location: UNC Friday Center, 100 Friday Center Drive, Chapel Hill, NC 27599

Co-Chairs: Drs. James Swenberg and Kenneth Mundt

Points for the discussions today:

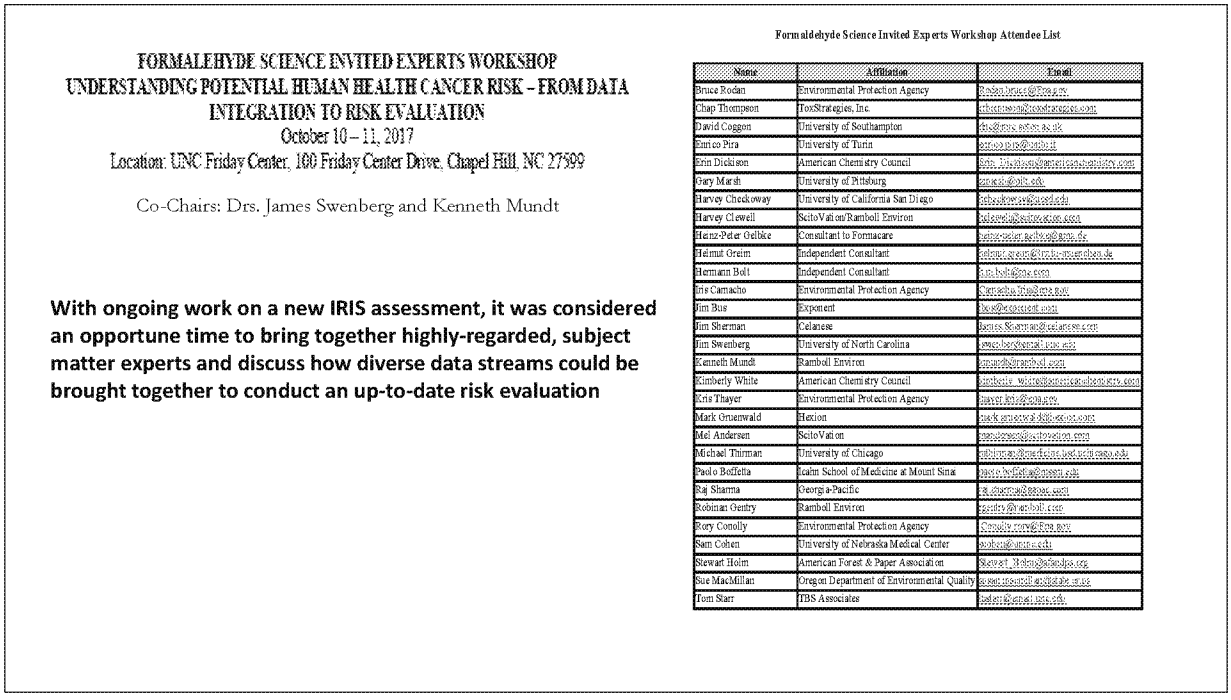
- Background about formaldehyde
- The current risk assessment landscape
- The meeting itself – goal, invitees, session structure, topics
- Overview of some of the conclusions/recommendations from the meeting
- Recommendations for integrating data streams into a formaldehyde risk evaluation

Some Background about Formaldehyde

- At concentrations above 6 ppm in rats, where there is clear cytotoxicity and cell replication, it causes nasal cancer in rats.
- One of the most extensively studied chemical carcinogens
- Present in all cells at an appreciable level - tenths of mmoles/liter
- Estimated background exhaled concentrations of several ppb
- Endogenous formaldehyde-DNA reaction products have a high background
- Inconsistent epidemiology in occupational cohorts
- Risk assessments across the world are highly divergent

A View of the Risk Assessment Landscape

ORGANIZATION	POPULATION	APPROACH	RISK LEVEL	Basis of Decision
EU/ECHA	General	Qualitative but not low-dose linear	No convincing evidence of a carcinogenic effect at distant sites	Causes tumors above a threshold concentration by mechanisms that are initiated by the cytotoxic effects but …data does not allow firm conclusion on a threshold-mode of action"
Health Canada	General	Threshold Carcinogen DSL Low priority substance	**2.3×10^{-10} at 1 ppb**	Carcinogenic hazard to humans "…under conditions that induce cytotoxicity and sustained regenerative cell proliferation."
Occupational Standards from various bodies In the US and EU	Workers	Threshold Carcinogen	Exposure standards: TWAs with STELs 0.1 ppm ACGIH; 0.016 pp NIOSH; NIOSH; 3ppm MAK and SCOEL	Varied: from MAK - Cancer classification 4: non-genotoxic; cell proliferation important to MoA to ACGIH's "cancer classification A1: confirmed human carcinogen "
NTP Report on Carcinogens (2011)		Qualitative	Known human carcinogen	Sufficient evidence in humans for nasal tumors and myeloid leukemia
IARC Monographs 10F (2010)		Qualitative	Known human carcinogen	Sufficient evidence in humans for tumors at both sites
IRIS (2010)	General	Low dose linear	**1×10^{-4} at 1 ppb**	For NPC, mutagenic MoA operating in conjunction with key event of formaldehyde cytotoxicity-induced cell proliferation, sufficient evidence of causal association for NPC and LHP cancer in humans



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With ongoing work on a new IRIS assessment, it was considered an opportune time to bring together highly-regarded, subject matter experts and discuss how diverse data streams could be brought together to conduct an up-to-date risk evaluation

Formaldehyde Science Invited Experts Workshop Attendee List

Name	Affiliation	Email
Bruce Rodan	Environmental Protection Agency	rodan.bruce@epa.gov
Chap Thompson	ToxStrategies, Inc.	cthompson@toxstrategies.com
David Coggon	University of Southampton	dnc@mrc.soton.ac.uk
Enrico Pira	University of Turin	enrico.pira@unito.it
Erin Dickison	American Chemistry Council	Erin_Dickison@americanchemistry.com
Gary Marsh	University of Pittsburg	Garym@pitt.edu
Harvey Checkoway	University of California San Diego	hcheckoway@uw.edu
Harvey Clewell	ScitoVation/Ramboll Environ	hclewell@scitovation.com
Heinz-Peter Gelbke	Consultant to Formacare	heinz-peter.gelbke@gmx.de
Helmut Greim	Independent Consultant	helmut.greim@mytum-muenchen.de
Hermann Bolt	Independent Consultant	hm.bolt@gmx.com
Iris Camacho	Environmental Protection Agency	Camacho.Iris@epa.gov
Jim Bus	Exponent	jbus@exponent.com
Jim Sherman	Celanese	James.Sherman@celanese.com
Jim Swenberg	University of North Carolina	jswenberg@email.unc.edu
Kenneth Mundt	Ramboll Environ	kmundt@ramboll.com
Kimberly White	American Chemistry Council	Kimberly_White@americanchemistry.com
Kris Thayer	Environmental Protection Agency	thayer.kris@epa.gov
Mark Gruenwald	Hexion	mark.gruenwald@hexion.com
Mel Andersen	ScitoVation	mandersen@scitovation.com
Michael Thirman	University of Chicago	mthirman@medicine.bsd.uchicago.edu
Paolo Boffetta	Icahn School of Medicine at Mount Sinai	paolo.boffetta@mssm.edu
Raj Sharma	Georgia-Pacific	RKSharma@gapac.com
Robinan Gentry	Ramboll Environ	rgentry@ramboll.com
Rory Conolly	Environmental Protection Agency	Conolly.rory@epa.gov
Sam Cohen	University of Nebraska Medical Center	scohen@unmc.edu
Stewart Holm	American Forest & Paper Association	Stewart_Holm@afandpa.org
Sue MacMillan	Oregon Department of Environmental Quality	susan.macmillan@deq.state.or.us
Tom Starr	TBS Associates	tstarr@chapel.net.edu

Four regulatory scientist – Bruce Rodan, Kris Thayer, Iris Camacho and Sue McMillan – and one EPA scientist from NHEEL – Rory Conolly.

FORMALDEHYDE SCIENCE INVITED EXPERTS WORKSHOP
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TUESDAY, OCTOBER 10, 2017	
Time	Item
7:00am – 8:00am	BREAKFAST (UNC Friday Center – Main Vestibule and Dining Area)
8:00am – 9:00am	REGISTRATION (Outside of Conference Room: Executive Mountain Level)
9:00am -9:05am	Welcome and Logistics - Kimberly White and Jim Swenberg (5 minutes)
9:05am -9:10am	Workshop Purpose and Objectives - Ken Mundt (5 minutes)
9:10am -9:25am	Understanding the Formaldehyde Science and Putting the Puzzle Pieces Together – Integrating New Science into Risk Evaluation Processes - Robinan Gentry (15 minutes)
9:25am – 9:40am	Summary of Global Risk Assessment Approaches for the Formaldehyde Science - General Approaches in EU, Canada, WHO and the US - Jim Bus (15 minutes)
SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY (Chair: Bernie Gross)	
9:40am – 10:00am	European Approach for Evaluating the Formaldehyde Science: OEL, Nasal Impacts and Threshold Assessment - Hermann Bolt (20 minutes)
10:00am -10:20am	Formaldehyde and Nasal Carcinogenicity: What Does the Epidemiology and Animal Data Tell Us? - Gary Marsh (20 minutes)
10:20am – 12:00pm	Discussion – Key Views by Participants on Charge Questions and MOA Framework • Charge Question #1 Discussion (25 minutes) • Charge Question #2 Discussion (25 minutes) • Charge Question #3 Discussion(25 minutes) • Open Discussion (25 minutes)
12:00pm – 1:00pm	LUNCH (UNC Friday Center – Main Vestibule and Dining Area)
SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY (Chair: Ken Mundt)	
12:45pm – 1:05pm	Key Events and Considerations for LHP Cancers - Ken Mundt (20 minutes)
1:05pm – 1:25pm	Overview: Epidemiology Evidence - Harvey Checkoway (20 minutes)
1:25pm – 1:45pm	Overview of the Animal Science - Chad Thompson (20 minutes)
1:45pm – 2:05pm	LHP Cancers and Biological Plausibility – Can Exogenous Formaldehyde Reach the Bone Marrow? Jim Swenberg (20 minutes)
2:05pm – 3:45pm	Discussion – Key Views by Participants on Charge Questions and MOA Framework • Charge Question #4 Discussion (25 minutes) • Charge Question #5 Discussion (25 minutes). • Charge Question #6 Discussion (25 minutes) • Open Discussion (25 minutes)
3:45pm – 4:00pm	BREAK (UNC Friday Center – Main Vestibule and Dining Area)
4:00pm – 4:15pm	Looking Across Data Streams to Draw Conclusions Regarding Causality: Key Considerations in the Formaldehyde Science Harvey Clewell (15 minutes)
4:15pm – 5:30pm	Discussion – Key Views by Participants on Charge Questions • Charge Question #7 Discussion (30 minutes) • Charge Question #8 Discussion (30 minutes) • Open Discussion (15 minutes)
5:30pm	ADJOURN DAY 1 OF WORKSHOP
6:45pm – 8:00pm	DINNER – OFFSITE (Location: TBD)

WEDNESDAY, OCTOBER 11, 2017	
Time	Item
7:30am – 8:00am	BREAKFAST (UNC Friday Center – Main Vestibule and Dining Area)
8:00am – 8:30am	REGISTRATION (Outside of Conference Room: Executive Mountain Level)
SESSION 3: FORMALDEHYDE –DATA RICH CHEMICAL RIPE FOR RISK EVALUATION? (Chair: Jim Sherman)	
8:00am – 9:15am	Overview of State-of-the-Science Approaches for Data Integration - Kimberly White (15 minutes)
9:15 – 9:30am	Recap of Day 1 Discussion: Identified Data Gaps and Uncertainties - Information Needs for a Formaldehyde Risk Evaluation Mel Andersen (15 minutes)
9:30am – 11:45am	Discussion – Key Views by Participants on Charge Questions • Charge Question #9 Discussion (20 minutes) • Charge Question #10 Discussion (30 minutes) • Charge Question #11 Discussion (30 minutes) • Charge Question #12 Discussion (20 minutes) • Charge Question #13 Discussion (20 minutes) • Open Discussion (15 minutes)
11:45am – 12:00pm	Workshop Wrap and Next Steps
12:00pm	LUNCH (UNC Friday Center – Main Vestibule and Dining Area)
1:00pm	ADJOURN DAY 2 OF WORKSHOP

SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY

1. Does the available scientific evidence support a specific MOA and causal association with NPC?
   - What mechanistic evidence is available to support the proposed modes of action frameworks discussed for NPC? What are the uncertainties?

   Suggested Discussants for Charge Question: Mel Andersen, Hermann Bolt , Harvey Clewell, Rory Conolly, Gary Marsh

2. What are the key animal data for characterizing the shape of the dose-response curve for formaldehyde-induced nasal tumors? What are the key epidemiological studies for formaldehyde-induced nasal tumors and how would you reconcile differences between those studies?
   - If a causal association can be established for human, what exposure metrics are associated with evidence of carcinogenicity? Is there evidence of a threshold for NPC in humans?

   Suggested Discussants for Charge Question: Mel Andersen, Hermann Bolt, Harvey Clewell, , Rory Conolly, Peter Gelblke, Helmut Greim, Gary Marsh

3. What quantitative methods (e.g., linear and non – linear low dose extrapolation, threshold, PBPK modeling for dose-response assessment) would best characterize the potential for NPC risk in humans?
   - Are there uncertainties with any of these quantitative methods that suggest this type of modeling should not be applied?

   Suggested Discussants for Charge Question : Harvey Clewell, Rory Conolly, Robinan Gentry, Tom Starr

SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY

4. What does the totality of the animal and epidemiology evidence tell us about the potential for a causal association with LHP and what conclusions can be drawn?
   - What role does endogenous production play in drawing conclusions regarding LHP?
   - Do the available data support a specific mode of action for hematopoietic cancers?

   Suggested Discussants for Charge Question: Paolo Boffetta, Harvey Checkoway, David Coggon, Sam Cohen, Robinan Gentry, Joseph Haney, Enico Pira, Jim Swenberg, Michael Thurman, Chad Thompson

5. What mechanistic data are critical to understanding a causal association between formaldehyde exposure and specific hematopoietic cancers?
   Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg Michael Thurman

6. Do epidemiology studies provide useful dose-response data for LHP?
   Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg Michael Thurman

7. What methods for assessing causality and evidence integration are best applied to the available data for LHP cancer for conducting a hazard assessment (e.g., Bradford Hill criteria, biological systems approach, hypothesis based weight of evidence framework, systematic review, combination of approaches?)
   Suggested Discussants for Charge Question: Mel Andersen, Paulo Boffetta, Harvey Checkoway, David Coggon, Kan Mundt, , Enrico Pira, Kris Thayer

8. What uncertainties are important for consideration when integrating the available evidence? **Suggested Discussants for Charge Question:** Mel Anderson, Jan Bus, Harvey Clewell, Sam Cohen, Robinan Gentry, Tom Starr

SESSION 3- FORMALDEHYDE –DATA RICH CHEMICAL RIPE FOR RISK EVALUATION?

9. What should be considered as the problem formulation and questions to be addressed when conducting a formaldehyde risk evaluation?

10. What are the best available approaches to conduct a robust evaluation of formaldehyde carcinogenic potential?

11. How can the approaches used to evaluate and integrate scientific evidence inform the risk assessment?
    - What aspects of the Biological Systems Approach can be used to integrate the formaldehyde data?
    - How can hypothesis based weight of evidence approach be to integrate the data streams for determination of causality?

12. What needs to be added or changed in the draft IPCS Mode of Action Framework nasal carcinogenicity?

13. What is the comparative weight of evidence for each hypothesized mode of action for nasal carcinogenicity?

Suggested Discussants for All Charge Questions – All Participants

Today, we want to convey a sense of the discussions, conclusions and recommendations from the group for the path forward

I. Dr. Swenberg - formaldehyde DNA-reaction products in various tissues from rodents and monkeys and their implications for responses to formaldehyde beyond the front of the nose.

II. Dr. Mundt – key recent epidemiological evaluations related to NPC, AML and Mode of Action

III. Dr. Andersen – recommendation for integrating the rodent and human studies into a more quantitative risk evaluation for formaldehyde.

I. Dr. Swenberg - formaldehyde DNA-reaction products in various tissues from rodents and monkeys

Formaldehyde-Induced DNA-Protein Crosslinks

- DNA-Protein Crosslinks (DPCs) have long been known to be genotoxic.
- Heck and Casanova conducted extensive studies on rats and primates exposed to radiolabeled formaldehyde.
- We have now developed a chemical-specific method for the dG-OHMe-cysteine DPC that can measure both endogenous and exogenous DPC.

Time to Steady-State for Exogenous [$^{13}CD_2$]-HO-CH2-dG Adducts in Nasal Epithelium

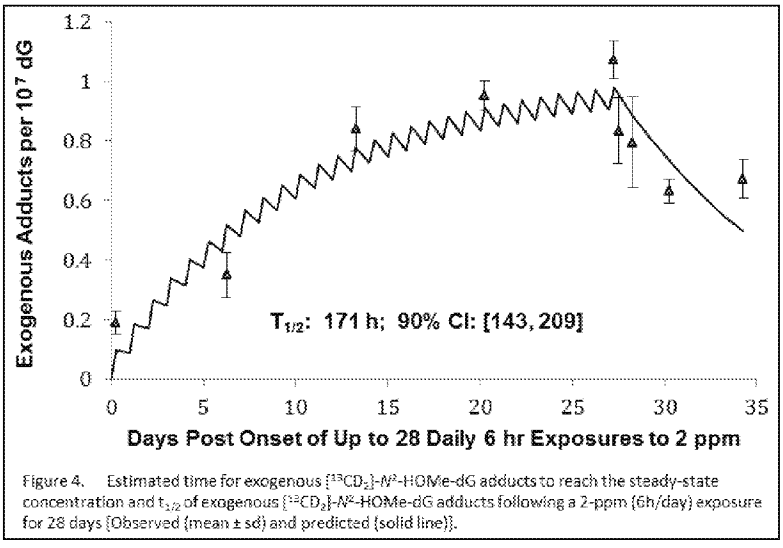
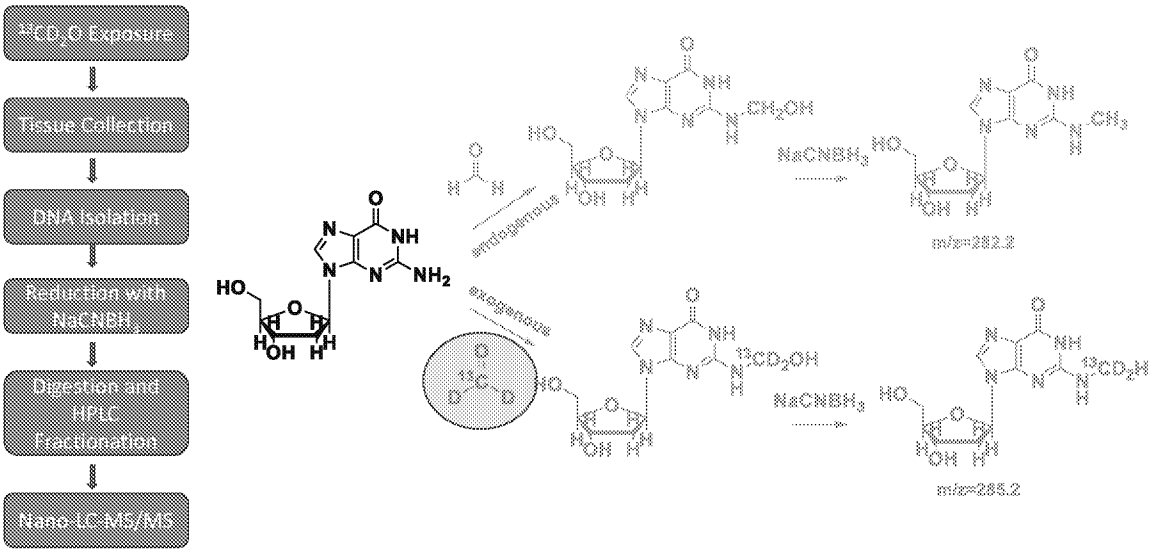


Figure 4. Estimated time for exogenous [$^{13}CD_2$]-N^2-HOMe-dG adducts to reach the steady-state concentration and $t_{1/2}$ of exogenous [$^{13}CD_2$]-N^2-HOMe-dG adducts following a 2-ppm (6h/day) exposure for 28 days (Observed (mean ± sd) and predicted (solid line)).

Looking at *Adducts* originating from both endogenous and exogenous formaldehyde.

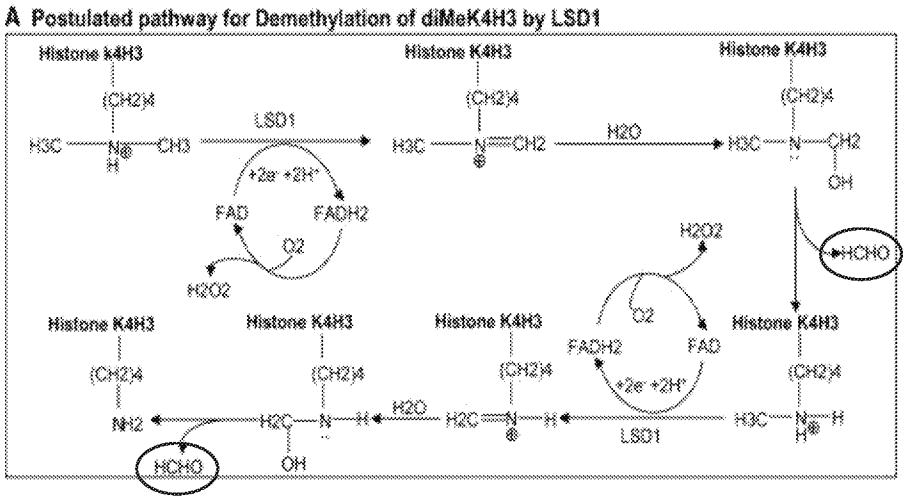


Formation of N^2-HOMe-dG mono-adducts (mean ± SD) in rat nasal epithelium, bone marrow and white blood cells exposed to 2-ppm labeled formaldehyde for 28 days.

Exposure period	Rat nasal epithelium N^2-HOMe-dG (adducts/10^7 dG)			Rat bone marrow N^2-HOMe-dG (adducts/10^7 dG)			Rat white blood cells N^2-HOMe-dG (adducts/10^7 dG)		
	Endogenous [a]	Exogenous	n	Endogenous [a]	Exogenous	n	Endogenous [a]	Exogenous	n
7 days	2.51 ± 0.63	0.35 ± 0.17	5	3.37 ± 1.56	n.d.	6	2.62 ± 1.12	n.d.	4
14 days	3.09 ± 0.98	0.84 ± 0.17	5	2.72 ± 1.36	n.d.	6	2.26 ± 0.46	n.d.	4
21 days	3.34 ± 1.06	0.95 ± 0.11	5	2.44 ± 0.96	n.d.	6	2.40 ± 0.47	n.d.	4
28 days	2.82 ± 0.76	1.05 ± 0.16	6	3.43 ± 2.20	0.34 [b]	12	2.49 ± 0.50	n.d.	4
28 days + 6h post expo	2.80 ± 0.58	0.83 ± 0.33	9	2.41 ± 1.14	n.d.	6	2.97 ± 0.58	n.d.	4
28 days + 24h post expo	2.98 ± 0.70	0.80 ± 0.46	9	4.67 ± 1.84	n.d.	5	2.57 ± 0.58	n.d.	4
28 days + 72h post expo	2.99 ± 0.63	0.63 ± 0.12	9	5.55 ± 0.76	n.d.	6	1.75 ± 0.26	n.d.	4
28 days + 168h post expo	2.78 ± 0.48	0.67 ± 0.20	10	2.78 ± 1.94	n.d.	4	2.61 ± 1.22	n.d.	4
Air control	2.84 ± 0.54	n.d.	8	3.58 ± 0.99	n.d.	6	2.76 ± 0.66	n.d.	6

[a] No statistically significant difference was found using the two-sided Dunnett's test (multiple comparisons with a control) (Dunnett, 1964). [b] The amount of exogenous N^2-HOMe-dG adducts that was found in only one bone marrow sample analyzed by AB SCIEX Triple Quad 6500. n.d. = not detected.

Some of the Endogenous Formaldehyde Arise from Demethylation of Histone 3 in the Nucleus



Shi *et al.* Cell, 2004 ; 119(7):941-953. (Cited over 1,100 times)

dG-Me-Cys in Rats Exposed to High Levels of Formaldehyde

Rats Exposed to 15 ppm

Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of rats exposed to **15 ppm of formaldehyde (6 h per day)**

Tissue	Exposure period (day)	dG-Me-Cys (crosslink/10^8 dG)	
		Endogenous	Exogenous
Nose	0	6.50 ± 0.30 (n=5)	ND*
	1	4.42 ± 1.10 (n=6)	5.52 ± 0.80
	2	4.28 ± 2.34 (n=6)	4.69 ± 1.76
	4	3.67 ± 0.80 (n=6)	18.38 ± 7.23
PBMC	0	4.98 ± 0.61 (n=5)	ND
	1	3.26 ± 0.73 (n=4)	ND
	2	3.00 ± 0.98 (n=5)	ND
	4	7.19 ± 1.73 (n=5)	ND
Bone Marrow	0	1.49 ± 0.43 (n=3)	ND
	1	1.67 ± 0.18 (n=3)	ND
	2	1.66 ± 0.57 (n=3)	ND
	4	1.41 ± 0.21 (n=3)	ND

* ND, Not detected

Similar responses are seen in Primates

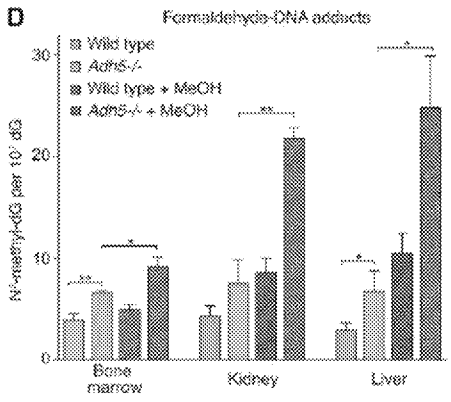
Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of primates exposed to 6 ppm of formaldehyde (6 h per day)

Tissue	Exposure period (day)	dG-Me-Cys (crosslink/10^8 dG)	
		Endogenous	**Exogenous**
Nose	0	3.59 ± 1.01 (n=5)	ND
	2	3.76 ± 1.50 (n=5)	1.36 ± 0.20
PBMC	0	1.34 ± 0.25 (n=5)	ND
	2	1.57 ± 0.58 (n=4)	ND
Bone Marrow	0	2.30 ± 0.30 (n=4)	ND
	2	1.40 ± 0.46 (n=5)	ND
Liver	0	15.46 ± 1.98 (n=6)	ND
	2	11.80 ± 2.21 (n=6)	ND

* ND, Not detected

Formaldehyde derived DNA reaction products in various tissues from formaldehyde precursors

- A variety of compounds are metabolized to formaldehyde – e.g., methanol, caffeine, aspartame, many drugs.
- Tissue formaldehyde adducts are found after with dosing mice methanol.
- With formaldehyde, no DNA-adducts are found at sites other than in the front of the nose in either rats or the non-human primates.
- **Inhaled formaldehyde does not reach these other tissues**



Pontel *et al.* Molecular Cell, 2015; 60(1):177-188

Ongoing Studies on Formaldehyde DNA-reaction products

- Low dose exposures in rats (air control, 1 ppb, 30 ppb, 300 ppb)
- Breath analysis shows approximately 1-2 ppb in humans
- 1 ppb is approximately the same as breath analysis with no exposure to formaldehyde
- Expected completion of mass spectrometry by January 2018

II. Key New Epidemiological Evidence/Analyses: NPC, AML and Mode of Action – Dr. Kenneth Mundt

- Marsh et al. (2014, 2016) challenge conclusion of NPC association as "neither consistent with the available data nor with other research findings"
  - "driven heavily by anomalous findings in one study plant (Plant 1)"
  - Nasal/sinus cancers seemed more plausible than NPC, but increased risk not seen.
- Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009)
  - Separated myeloid leukemias into acute (AMLs) and chronic (CML)
  - Associations seen with Hodgkin lymphoma and CML, but not observed in other studies
  - Evaluated associations with "peak" exposure
- Gentry et al. (2013) and Mundt et al. (2017) reanalysis of Zhang et al. (2010) demonstrate no association between formaldehyde exposure and any reported outcome among exposed workers.

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No excess mortality from AML or CML observed

	Checkoway et al. 2015				Beane Freeman et al. 2009			
	Non-exposed (n=3,136)		Exposed (n=22,483)		Non-exposed (n=3,108)		Exposed (n=22,511)	
	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Myeloid leukemia	4	**0.69** (0.19-1.76)	44*	**0.86** (0.64-1.16)	4	**0.65** (0.35–1.74)	44	**0.90** (0.67–1.21)
AML	4	**0.93** (0.25-2.37)	30	**0.80** (0.56-1.14)	NR		NR	
CML	0		13	0.97 (0.56-1.67)	NR		NR	

US mortality rates used as the reference

*One death was coded to ICD-8 205.9, unspecified myeloid leukemia.

Association between peak exposure and mortality using most specific diagnosis (Checkoway et al. 2015)

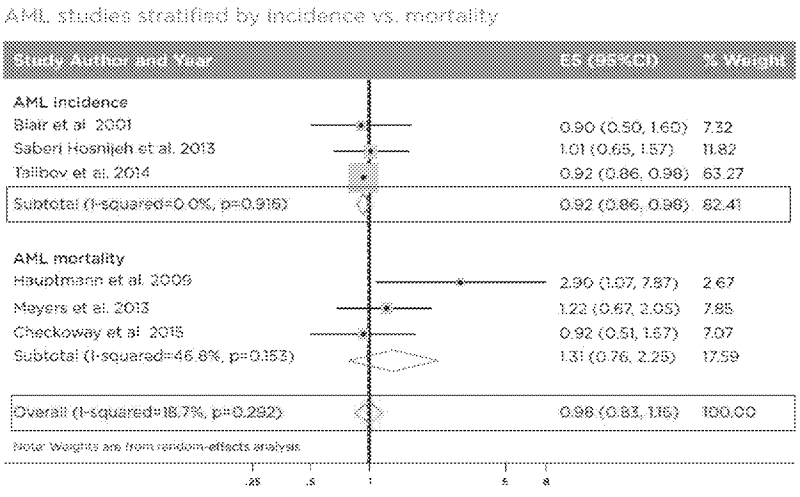
	No peak		≥2.0 to < 4.0 ppm		≥4.0 ppm		
Diagnosis	Obs	HR (95% CI)	Obs	HR (95% CI)	Obs	HR (95% CI)	P trend
Hodgkin lymphoma	15	1.0 (referent)	5	2.18 (0.77-6.19)	7	3.38 (1.30-8.81)	0.01
Myeloid leukemia	27	1.0 (referent)	11	2.09 (1.03–4.26)	10	1.80 (0.85–3.79)	0.06
AML	**21**	**1.0 (referent)**	**7**	**1.71 (0.72–4.07)**	**6**	**1.43 (0.56–3.63)**	**0.31**
CML	**6**	**1.0 (referent)**	**3**	**2.62 (0.64–10.66)**	**4**	**3.07 (0.83–11.40)**	**0.07**

Of 13 AML deaths with peak >2.0 ppm, only 4 had any peak within the 20 years of death; **only 1 AML death occurred (similar to expected) within 2 to** 15 years (typical latency window).

Uncertain relevance of exposure measure – predicted peak exposure – with no measures of actual exposures

20

No increased risk of AML is seen in relation to occupational exposure to formaldehyde



21

More complete analysis of Zhang et al. 2010 data

- Zhang et al. (2010) reported significant "changes"* in blood parameters and aneuploidy in in vitro cell cultures.
- Concluded, "formaldehyde exposure can have an adverse effect on the hematopoietic system and that ***leukemia induction by formaldehyde is biologically plausible***, which heightens concerns about its leukemogenic potential from occupational and environmental exposures."

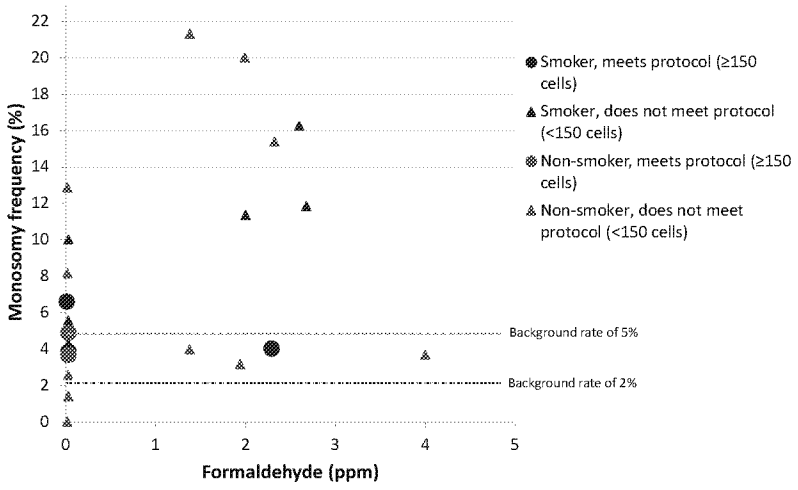
*Study was cross-sectional and reported differences in blood parameters between exposed and unexposed workers were measured at one point in time: no changes were investigated over times (boldface emphasis added).

Association between formaldehyde exposure and WBC and RBC counts and components do not show expected dose-response

Exposure	Blood Count Adjusted RR	95% CI	†p-value	Blood Count Adjusted RR	95% CI	†p-value
	WBC			**RBC**		
Unexposed	1.00			1.00		
<1.3 ppm	***0.87**	0.78-0.97		***0.94**	0.91-0.98	
≥1.3 ppm	***0.85**	0.76-0.96	0.943	***0.94**	0.90-0.98	0.947
	Lymphocytes			**Hemoglobin**		
Unexposed	1.00			1.00		
<1.3 ppm	***0.85**	0.75-0.96		0.98	0.94-1.01	
≥1.3 ppm	***0.79**	0.69-0.90	0.660	0.99	0.95-1.03	0.818
	Monocytes			**MCV**		
Unexposed	1.00			1.00		
<1.3 ppm	0.90	0.77-1.06		1.03	0.99-1.08	
≥1.3 ppm	0.89	0.75-1.04	0.973	1.06	1.02-1.11	0.550
	Granulocytes			**Platelets**		
Unexposed	1.00			1.00		
<1.3 ppm	0.87	0.75-1.01		***0.85**	0.75-0.96	
≥1.3 ppm	0.88	0.75-1.03	0.997	0.91	0.80-1.03	0.674

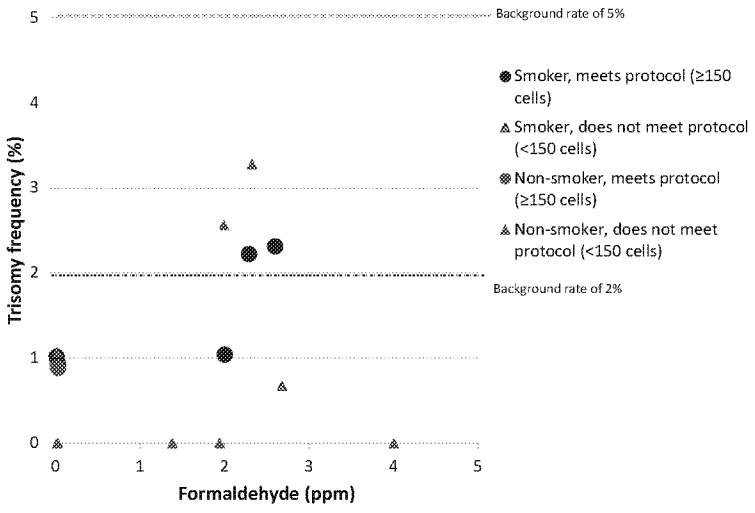
†Comparison between exposed categories
*p<0.05 compared with unexposed

Monosomy 7 – only colored circles met their own internal study protocol



24

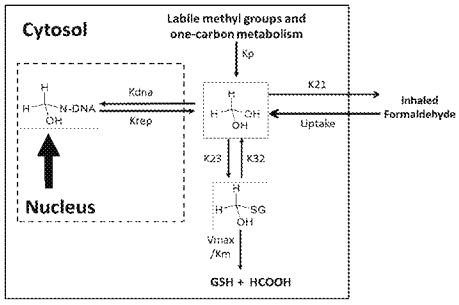
Trisomy 8 - only colored circles met their own internal study protocol



Epidemiological Conclusions

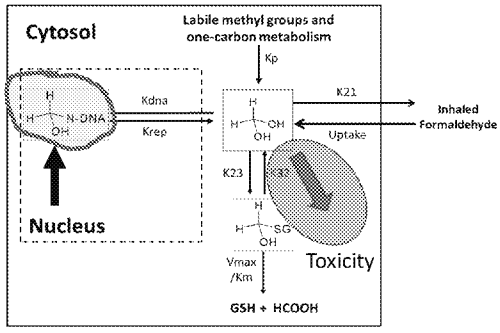
- Epidemiological evaluation of the one cluster of NPC deaths not clearly associated with formaldehyde exposure. Nasal/sino-nasal cancers seemed plausible based on animal studies but increased risk of these tumors has not been seen in the epidemiological studies.
- Conclusions relied upon from Beane Freeman et al. 2010, i.e., association between ML and 'peak' exposure were not verified upon more complete analysis:
  - No excess of ML or AML observed; and
  - Very few decedents with AML had any peak exposure (only 1 within usual latency period).
- Conclusions relied upon from Zhang et al. 2010 inconsistent with fuller analysis of study data, including unreported individual exposure measurements: no associations with exposure level seen among exposed.
- **Weight of evidence synthesis of epidemiological evidence provides vert little support for a causal association between formaldehyde and either NPC or AML.**

III. Integrating studies into a more quantitative risk evaluation



Background: Formaldehyde flux, primarily from tissue to air, with significant background levels of various formaldehyde reaction products

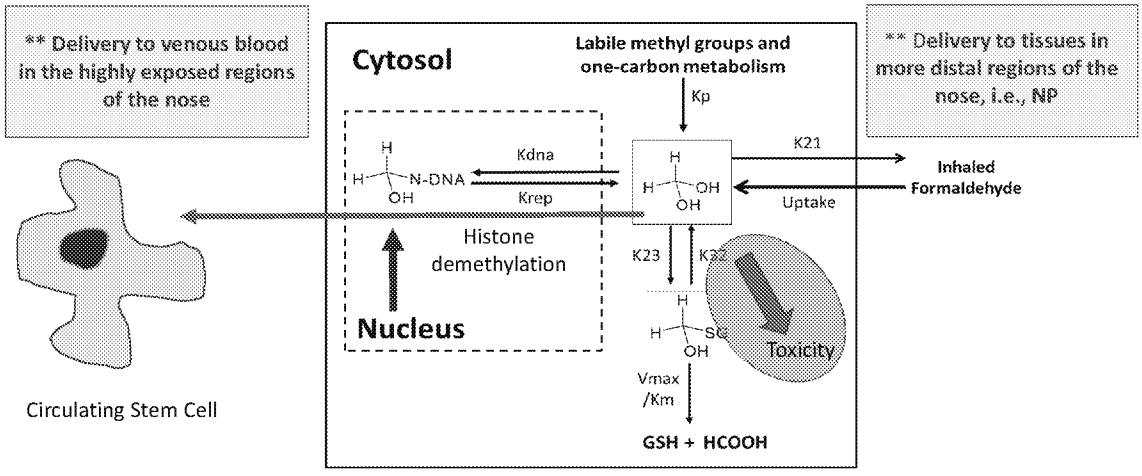
Exposed: Formaldehyde flux, primarily from air to tissue, increases tissue concentration leading to cytotoxicity and increased level of DNA-reaction products



Recommendations/Conclusions: Mode of Action

- The risk assessment for formaldehyde should be structured around a MOA framework based on the extensive understanding of cancer causation in the rat nose
- Measures of DNA-reaction products from formaldehyde should be central considerations in evaluating the ability of inhaled formaldehyde to reach other tissues
- The BBDR model for formaldehyde by Conolly and others could be updated to assist in answering questions about the relative roles of cytotoxicity and DNA-reactivity in cancer in the rat

What would be the proposed MOA for human cancer in light of central role of high doses and cytotoxicity?



** Dosimetry studies indicate that it unlikely that high tissue concentrations can be achieved in any of these more remote tissues.

Recommendations/Conclusions: NP Cancer Epidemiology

- The association of NPC with formaldehyde exposure needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde and the presence of relatively high concentrations in all cells.
- Review experience with other human nasal carcinogens to determine whether there are reasons to expect differential sensitivity in particular portions of the human nose compared to the rat.

Recommendations/Conclusions: LHP Cancer Epidemiology

- The association of LHP cancer also needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde adding to an already substantial level of cellular formaldehyde.
- Evaluate experience with other other compounds producing leukemia, such as benzene and chemotherapeutic compounds, where bone marrow toxicity is also evident.

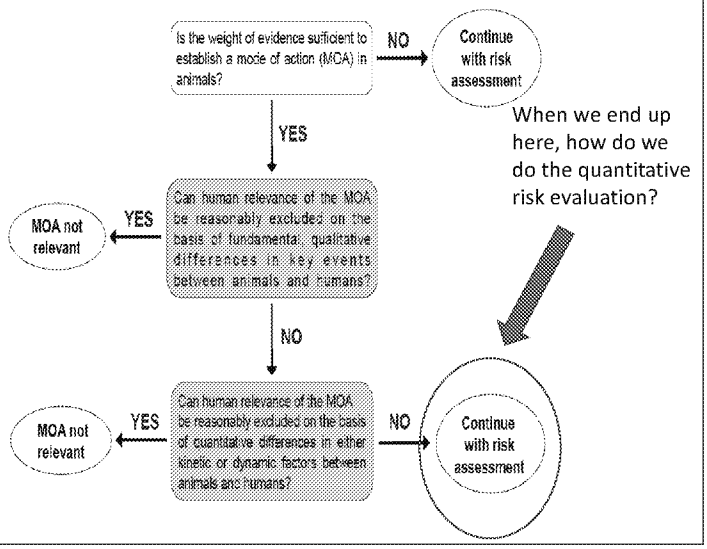
Systematic review is more than just assessing modes-of-action

THE IPCS CONCEPTUAL MOA FRAMEWORK FOR EVALUATING ANIMAL CARCINOGENESIS:

Introduction to the Framework Analysis

- Postulated mode of action (theory of the case)
- Key events
- Concordance of dose-response relationships
- Temporal association
- Strength, consistency and specificity of association of tumour response with key events
- Biological plausibility and coherence
- Other modes of action
- Uncertainties, Inconsistencies, and Data Gaps
- Assessment of postulated mode of action

IPCS general scheme illustrating the main steps in evaluating the human relevance of an animal MOA for tumour formation.



When we end up here, how do we do the quantitative risk evaluation?

Recommendations/Conclusions: The Integrated Risk Evaluation:

- The risk assessment should take into account the weight of evidence for causation of a response by formaldehyde, the concentrations in air and tissues associated with these effects, and the overall evidence for particular modes of action.
- Systematic review needs to evaluate both the qualitative evidence for various MOAs and the manner in which the studies are brought together to support extrapolation models – threshold or low-dose linear - in the quantitative risk assessment.
- This type of robust evaluation appears beyond the scope of present systematic reviews that focus on toxicity rather than the support for extrapolation models based on mode of action studies.

The oarticipants

Some recent references

- Albertini, R. J., & Kaden, D. A. (2017). Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?. Critical reviews in toxicology, 47(2), 145-184.
- Checkoway, H., Boffetta, P., Mundt, D. J., & Mundt, K. A. (2012). Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies. Cancer Causes & Control, 23(11), 1747-1766.
- Checkoway, H., Dell, L. D., Boffetta, P., Gallagher, A. E., Crawford, L., Lees, P. S., & Mundt, K. A. (2015). Formaldehyde exposure and mortality risks from acute myeloid leukemia and other Lymphohematopoietic Malignancies in the US National Cancer Institute cohort study of workers in Formaldehyde Industries. Journal of occupational and environmental medicine, 57(7), 785.
- European Food Safety Authority (2014). Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. EFSA Journal, 12(2), 3550.
- Lai, Y., Yu, R., Hartwell, H. J., Moeller, B. C., Bodnar, W. M., & Swenberg, J. A. (2016). Measurement of Endogenous versus Exogenous Formaldehyde-Induced DNA-Protein Crosslinks in Animal Tissues by Stable Isotope Labeling and Ultrasensitive Mass Spectrometry. Cancer research, 76(9), 2652-2661.
- Mundt, K. A., Gallagher, A. E., Dell, L. D., Natelson, E. A., Boffetta, P., & Gentry, P. R. (2017). Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells?. Critical Reviews in Toxicology, 1-11.
- Mundt KA, Gentry PR, Dell LD, Rodricks JV, Boffetta P. (2017). Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity. Regul Toxicol Pharmacol. Nov 17.
- Pontel, L. B., Rosado, I. V., Burgos-Barragan, G., Garaycoechea, J. I., Yu, R., Arends, M. J., ... & Swenberg, J. A. (2015). Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen. *Molecular cell*, *60*(1), 177-188.
- Swenberg, J. A., Moeller, B. C., Lu, K., Rager, J. E., Fry, R. C., Starr, T. B. (2013). Formaldehyde carcinogenicity research: 30 years and counting for mode of action, epidemiology, and cancer risk assessment. Toxicol Pathol, 41, 181- 9.
- Yu, R., Lai, Y., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., ... & Swenberg, J. A. (2015). Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. *Toxicological sciences*, *146*(1), 170-182.

Message

From: Caldwell, Jane [Caldwell.Jane@epa.gov]
Sent: 5/15/2015 9:34:53 PM
To: Gibbons, Catherine [Gibbons.Catherine@epa.gov]; Fritz, Jason [Fritz.Jason@epa.gov]; Vulimiri, Suryanarayana [Vulimiri.Sury@epa.gov]; Sonawane, Bob [Sonawane.Bob@epa.gov]
Subject: Here is the formaldehyde section and the accompanying appendix
Attachments: Modes of action for Lymphoma revised draft 051515.docx; Appendix 1 lhp moa 051515.docx

Dear All,

As promised, here is a rewritten formaldehyde section and accompanying appendix. The section has been restructured as has been discussed in our meetings and from written comments. I have included new information to address studies not previously included and identified by Sury. I have also expanded the discussion of oxidative stress/hypoxia as Jason had correctly identified some work needing to be done there to tie this together more clearly.

Study specific analyses are in the appendix and need to be there. The appendix is not a redundant feature of the section writeup. The references for each differ as they do not contain the same information. I have done QA to make sure the references cited in each are specifically referenced for each.

Tables A and X have been updated and are in the Appendix.

Table Y is in the section writeup. I have added some material to it to reflect changes in the text.

I did not attempt to construct a figure as was done with McHale et al 2012 for benzene. I did not think it would be easy to make in a way that does not end up to be confusing. Perhaps later that can be discussed.

Have a nice weekend! I intend not to work on this one – unlike last weekend.

Jane Caldwell

Message

From: Fritz, Jason [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F8D42341BD2241598226069F9623074A-FRITZ, JASON]
Sent: 8/9/2016 4:37:28 PM
To: Kraft, Andrew [Kraft.Andrew@epa.gov]
CC: Glenn, Barbara [Glenn.Barbara@epa.gov]
Subject: Re: FYI ERC
Attachments: CoglianoERCcomments071116_JF.docx; WalkerTox Review_ERC_May2016_JF.docx

Heya,

So I've now tried both trying to make revisions in the draft on the IRIS formaldehyde assessment sharepoint site using "Word Online", as well as in Full word on my EPA Laptop, with no luck. The browser locks up during efforts to try and actually make revisions when using Word in the IE browser, and when I try to open the document using Word on my EPA laptop, it times out and says that "the network connection was interrupted", even though I can click through the file folder structure on the Onedrive site, surf the web, etc. So perhaps the file is just too large and is making things crash.

Tennille didn't have many comments in her annotated version of the draft, but I've indicated how I would respond in the attached doc. I've only have a summary doc of Vince's comments, but I've also indicated what we could do when he refers specifically to the LHP or URT MOA sections.

I haven't seen anyone else who specifically made comments on the URT or LHP MOA, but I didn't look through comments from the reviewers assigned to other sections.
Maybe chopping the FA TR into individual sections would allow people to work on them easier (i.e. "combine" commented sections from various authors into one document, especially for people who have submitted detailed revisions and suggestions)?

Jason

From: Kraft, Andrew
Sent: Thursday, July 28, 2016 4:29:29 PM
To: Fritz, Jason
Cc: Glenn, Barbara
Subject: FYI ERC

Teneille looked at the URT MOA section and had some suggestions. FYI

Appointment

From: Fritz, Jason [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F8D42341BD2241598226069F9623074A-FRITZ, JASON]
Sent: 5/21/2015 3:45:45 PM
To: Gibbons, Catherine [Gibbons.Catherine@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Caldwell, Jane [Caldwell.Jane@epa.gov]; Sonawane, Bob [Sonawane.Bob@epa.gov]; Vulimiri, Suryanarayana [Vulimiri.Sury@epa.gov]; Cogliano, Vincent [cogliano.vincent@epa.gov]
BCC: DCRoomPYN7771-North/ORD-NCEA-DC [DCRoomPYN7771@epa.gov]

Subject: FA LHP MOA draft markup discussion
Attachments: Modes of action for Lymphoma revised draft 051515.docx; Appendix 1 lhp moa 051515.docx
Location: DCRoomPYN7771-North/ORD-NCEA-DC

Start: 5/28/2015 1:00:00 PM
End: 5/28/2015 5:00:00 PM
Show Time As: Tentative

Hello everyone,

The purpose of this meeting is to go through the most recent revision (attached, from Jane C.) of the MOA/mechanistic event synthesis for the formaldehyde LHP cancer. I would like the focus to be on "big" picture changes, e.g. section organization, information content, clarity of presentation and arguments, consistency, background, speculation, etc.

To that end, everyone please read and become familiar with the revised draft synthesis section attached, prior to the meeting. This will be conducive to a good discussion and will facilitate stepping through important aspects of each section.

Modes of action for Lymphoma revis...

For reference, I am also attaching the Appendix which was provided by Jane to accompany this revised draft. This is FYI and may facilitate review/understanding of the MOA synthesis, but we will not be going over this section during the course of this markup meeting.

Appendix 1 lhp moa 051515.docx

Thanks, and we look forward to a constructive discussion next week!
Jason Fritz, TPWG co-chair

Appointment

From: Glenn, Barbara [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7A2DC9210D2D4D02A623B33F87F49436-GLENN, BARBARA]
Sent: 6/21/2016 2:47:37 PM
To: Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]
BCC: DCRoomPYS11771-Crystal [DCRoomPYS11771-Crystal@epa.gov]

Subject: Formaldehyde Issues
Attachments: Charge_Peer Review_062116.docx; EXECUTIVE SUMMARY - 10Jun2016DBsuggests.docx
Location: DCRoomPYS11771-Crystal

Start: 6/23/2016 5:00:00 PM
End: 6/23/2016 7:00:00 PM
Show Time As: Busy


Charge_Peer Review_062116....


EXECUTIVE SUMMARY - 10J...

Agenda and attachments

Charge questions
Executive summary
Probabilities

Appointment

From: Kavlock, Robert [Kavlock.Robert@epa.gov]
Sent: 4/26/2016 2:09:02 PM
To: Kavlock, Robert [Kavlock.Robert@epa.gov]; Olden, Kenneth [Olden.Kenneth@epa.gov]; Vandenberg, John [Vandenberg.John@epa.gov]; Cogliano, Vincent [cogliano.vincent@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Perovich, Gina [Perovich.Gina@epa.gov]; Gwinn, Maureen [gwinn.maureen@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]; Kadeli, Lek [Kadeli.Lek@epa.gov]; Deener, Kathleen [Deener.Kathleen@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Mazur, Sarah [Mazur.Sarah@epa.gov]
CC: IRIS Calendar [IRIS_Calendar@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]; Birchfield, Norman [Birchfield.Norman@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Corona, Elizabeth [Corona.Elizabeth@epa.gov]

Subject: Prebrief for Monthly IRIS Meeting - materials added
Attachments: Kavlock_Apr2016_bckgrnd.docx; HCHOBriefKavlock042816.pptx; IRIS6mo-2k16-05.doc; Kavlock BaP update_4-26-2016-cleancopy.docx
Location: 41213 RRB; call-in: 866-299-3188, code: 564-6620 (no 202)

Start: 4/28/2016 7:00:00 PM
End: 4/28/2016 8:00:00 PM
Show Time As: Busy

Recurrence: Monthly
the last Thursday of every 1 month(s) from 3:00 PM to 4:00 PM


Kavlock_Apr201...


HCHOBriefKavlo...


IRIS6mo-2k16-0...


Kavlock BaP update_4-26-201...

Message

From: Kraft, Andrew [Kraft.Andrew@epa.gov]
Sent: 3/23/2017 9:01:06 PM
To: Soto, Vicki [Soto.Vicki@epa.gov]
CC: Cunningham, Taukecha [Cunningham.Taukecha@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]
Subject: Formaldehyde Tox Review, Part "b"
Attachments: FormaldehydeTRdraftTechEdit032317_b.docx

Hooray!

Message

From: Kraft, Andrew [Kraft.Andrew@epa.gov]
Sent: 3/23/2017 8:59:54 PM
To: Soto, Vicki [Soto.Vicki@epa.gov]
CC: Cunningham, Taukecha [Cunningham.Taukecha@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]
Subject: Formaldehyde Tox Review, Part "a"
Attachments: FormaldehydeTRdraftTechEdit032317_a.docx

Please see the attached. Thank You!